RESOURCE HUB *Correspondents*

ASTMH 2021 Annual Meeting (virtual)

Complete series

MESA Correspondents bring you cutting-edge coverage from the ASTMH 2021 Annual Virtual Meeting

17 - 21 November 2021

Virtual Conference

The MESA Alliance would like to thank Divya Beri (Lindsley F. Kimball Research Institute, New York Blood Center, USA) for providing senior editorial support.

The MESA Alliance would also like to acknowledge the MESA Correspondents Edima Ottoho (Nigeria Liquefied Natural Gas-funded Bonny Malaria Elimination Project, Nigeria), Tope Kayode (Consultant, Nigeria), Franklin Tembongshu Formilack (University of Buea, Cameroon), Lucy W. Mwangi (University of Nairobi, Kenya), Vita Mithi (MESA Consultant, Malawi), Ana Alonso (Georgetown University), Faith Huge (Vrije University Brussels, Belgium), Olajoju Temidayo Soniran (Akanu Ibiam Federal Polytechnic, Nigeria), Isabelle Delrieu (EpiLinks, France), Doumbe Belisse Patricia (Yaoundé Research Institute of OCEAC, Cameroon) and Carlos A. Fernández Miñope (University of Antwerp, Belgium) for their crucial role in the reporting of the sessions.

Table of contents

Day 1: 17th November 2021

Day 1: Wednesday, 17th November 2021

The 70th Annual ASTMH virtual meeting started with the Young Investigator Award Sessions. These awards are given for work presented by young investigators to recognise their work and to encourage young scientists to pursue careers in tropical disease research.

Young Investigator Award Sessions A

1109 - Predictors and associations with maternal and birth outcomes of *Plasmodium falciparum* infection in the first trimester among nulliparous women from the Democratic Republic of the Congo, Kenya, and Zambia

Sequoia Leuba (Imperial College of London, United Kingdom) presented her research done with Dr. Patrick Walker. Leuba conducted a study on first-trimester malaria in pregnancy. It looked at potential factors associated with increased likelihood of first-trimester malaria, and the potential causal effects on adverse maternal and birth outcomes. Results showed that first-trimester malaria prevalence varied by transmission intensity and infections were very common in high transmission areas. The absence of consistent predictors suggested that routine parasite screening in early pregnancy may be needed to mitigate first-trimester malaria in high-prevalence settings. Non-significant associations of first-trimester malaria with higher prevalence of preterm birth, low birth weight, and anemia in late pregnancy suggest a possible need to develop prophylactic malarial medications for use in the first trimester.

Young Investigator Award Sessions B

0423 - Glycolipid-adjuvanted radiation-attenuated sporozoites improves the efficacy of a heterologous Prime-and-Trap malaria vaccine

Felicia N. Watson (University of Washington, United States of America) commenced her talk by highlighting the global malaria burden and how it has been exacerbated by this COVID-19 pandemic. She mentioned the role of pre-erythrocytic vaccines in fighting malaria. Her study focused on how to improve the translational potential of a liver stage vaccine that induces liver-resident memory CD8+ T (Trm) cells in experimental mice. She investigated methods to improve the translational potential of Prime-and-Trap by reducing the radiation-attenuated sporozoites (RAS) dose, eliminating the intravenous (IV) administration requirement, and adding a co-administered glycolipid adjuvant, 7DW8-5. She observed that 7DW8-5 has translational potential, Prime-and-Trap efficacy is durable with or without 7DW8-5 for at least 4 months, and co-administration of RAS + 7DW8-5 protected mice with a 4-fold lower dose and can protect after Prime-and-Trap when administered intradermally. Hence, this first generation Prime-and-Trap is a promising and easy to deliver vaccine strategy.

0443 - Rectal artesunate administration is associated with lower referral completion of children with suspected severe malaria in Nigeria and the Democratic Republic of the Congo

Nina Brunner (Swiss Tropical and Public Health Institute/ CARAMAL Consortium, Switzerland) research presentation was on rectal artesunate administration in children with suspected severe malaria. Rectal artesunate is a pre-referral treatment for children with suspected severe malaria, administered by either community health workers or health workers at primary health centres. Her

study was done in Nigeria, Uganda, and the Democratic Republic of Congo (DRC). The study findings revealed that rectal artesunate administration is associated with lower referral completion in DRC. In the study, referral completion was context specific and defined as children being brought at a referral facility.

0711 - Arthemether-lumefantrine antimalarial efficacy among adults on antiretroviral therapy in Malawi

Jernelle C. Miller (University of Maryland, United States of America) introduced her presentation by highlighting malaria burden and prevalence of HIV in Malawi. Miller's study hypothesized that the use of efavirenz (EFV)-based antiretroviral drug (ART) may impair efficacy of Artemether lumefantrine (AL) for malaria treatment in adult patients in a randomized controlled trial. A 28-day therapeutic efficacy study among participants with clinical malaria confirmed by blood smear was conducted according to World Health Organization protocol. Samples were analyzed using PCR for three polymorphic genes: merozoite surface protein 1 and 2, and glutamate-rich protein; followed by gel electrophoresis and monitoring plasma lumefantrine levels. Findings showed that AL was still efficacious (above 90% threshold), but plasma lumefantrine levels were below the recommended dose (200 ng/mL) in most study participants which suggested increased treatment failure risk.

1138 - Effectiveness and safety of intermittent preventive treatment for malaria using either Dihydroartemesinin-Piperaquine or Artesunate-Amodiaquine in reducing malaria related morbidities and improving cognitive ability in school-aged children in Tanzania: a controlled randomized trial

Geofrey Makenga (National Institute for Medical Research, Tanga, Tanzania) presented a randomized clinical control trial conducted in north-eastern Tanzania. The study showcased the effectiveness and safety of Dihydroartemisinin-Piperaquine (DP) and Artesunate-Amodiaquine (ASAQ) for intermittent preventive treatment of malaria and improving cognitive ability in school-aged (10-14 years) children (IPTsc), who have become increasingly more vulnerable compared to other age groups in the highly malaria endemic study areas. The IPTsc offered safe protection against malaria parasitaemia (78%), reduced malaria prevalence (from 26% to 9%) and anaemia, increased mean haemoglobin level, and was pragmatically feasible for scale-up in school health programmes if adopted as a policy.

Young Investigator Award Sessions C

0140 - Spatiotemporal overlapping of dengue, chikungunya, and malaria infections in children in Kenya

Aslam Khan (Stanford University, United States of America) highlighted the fact that malaria, chikungunya (CHIKV), and dengue (DENV) are endemic causes of fever among children in Kenya and are sustained by different mosquito vectors present in human settlements. Khan examined the spatiotemporal pattern and risk factors for exposure to malaria, CHIKV, and DENV in coastal and western Kenya. Over 5 years, the proportion of seropositive children was 9.8% for CHIKV, 5.5% for DENV and 39.1% for malaria. Hot-spots for all three diseases were identified in all sites as well as a frequent overlapping and higher seroprevalence for CHIKV and DENV in the less dense communities. The presence of litter and household overcrowding were linked to a higher risk of hot-spot occurrence; on the contrary, window screens and metal roofs were less likely to be found in hotspots. The results will be helpful to enhance surveillance activities and targeted control of these mosquito-borne diseases in Kenya.

0224 - High prevalence of asymptomatic malarial anemia and association with early clinical conversion in a Plasmodium falciparum hyper-endemic setting in Cameroon

Balotin Fogang (University of Yaounde I/Centre Pasteur Cameroon, Cameroon) started his talk by stating that less than one in twenty *Plasmodium falciparum* infections are symptomatic. Fogang studied the prevalence of asymptomatic malarial anaemia and its association with the appearance of clinical symptoms such as fever with *Plasmodium falciparum* infections in Cameroon (known as clinical conversion). Participants infected with *P. falciparum* were followed using a structured questionnaire over a 3 week period and mass testing using nested PCR served to diagnose peripheral malaria. Three out of four individuals sampled were asymptomatic *P. falciparum* positive (353 individuals sampled). Among the asymptomatic individuals, 15.4% reported having early clinical conversion before week 4 after testing, with gender and anaemic status as significant factors. High parasite density, and female gender were associated with the presence of asymptomatic malarial anemia. Asymptomatic malarial anemia was determined a key predictor of early development of febrile illness in the population. These findings highlight the need for better diagnostic tools for prompt early treatment of asymptomatic parasitaemia.

0314 - Efficacy of CDC light trap and human decoy trap (HDT) compared to human landing catch (HLC) for estimating malaria vector biting rates in rural Tanzania

Isaac Haggai Namango (Swiss Tropical and Public Health Institute, Switzerland and 2BC Centre for Excellence in HIV/AIDS, Canada) started the talk mentioning that among the traps used to capture biting mosquitoes, the human landing catch (HLC) is considered the standard method, although safety is of most concern and its deployment is labor consuming. Namango presented his results on the efficacy of CDC light trap and human decoy trap (HDT) as alternatives to indoor and outdoor HLC in Ulanga rural Tanzania. Over two years, mosquitoes were collected as part of an exercise to evaluate the impact of indoor residual spraying (IRS) using CDC light traps, HDT and HLC. *Culex spp* were the most abundant mosquitoes trapped by all three traps, followed by *An. funestus* and *An. arabiensis*. HDT caught far fewer *An. arabiensis*, and *An. funestus* compared to outdoor HLC and only a third of *Culex spp*. The efficacy of CDC light trap and HDT to estimate *Anopheles* biting varied greatly depending on mosquito density. CDC light trap and HDT were shown to be not suitable as HLC surrogates in the calculation of Anopheles biting rate in this region of Tanzania but its role in malaria vector surveillance should be interpreted carefully.

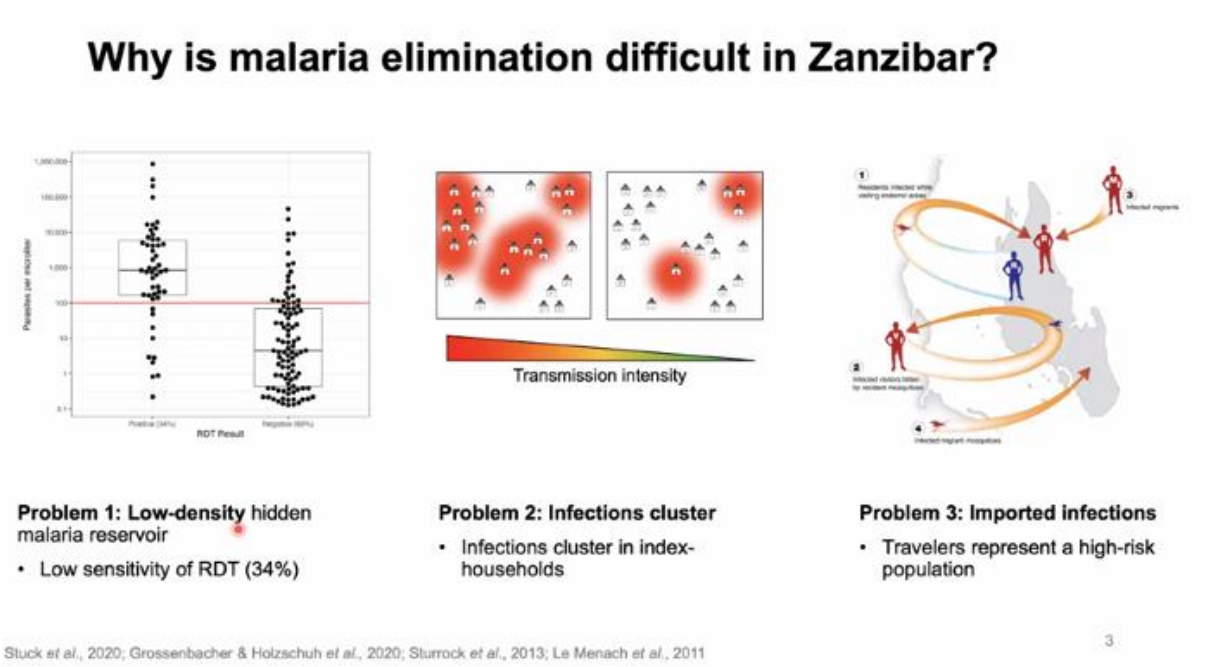
0647 - Risk Factors for Border Malaria in a Low Transmission Setting: A Case-Control Study in Jazan, Saudi Arabia

Shaymaa A. Abdalal (Tulane School of Public Health and Tropical Medicine, United States) started his talk by describing the study area, the Jazan region. Jazan region is located at the border between an almost malaria-free Saudi Arabia and high-risk communities along the border with Yemen. *Anopheles Arabiensis* is the sole vector responsible for malaria transmission and more than two-thirds of the population is mostly farmers who live in rural areas. Abdalal conducted an unmatched case-control study aiming to identify risk factors for border malaria in the Jazan region between December 2017 to January 2019. Over 30% of participants were positive for malaria infection. Among the factors investigated, male sex, animal husbandry, travelling away from their home village within the past 30 days and attending a night spiritual gathering appeared as independent risk factors for malaria infection. These results highlight the importance of addressing social and behavioral practices within malaria elimination programs.

Young Investigator Award Sessions D

0248 - Understanding residual *P. falciparum* transmission in Zanzibar through multiplexed amplicon deep sequencing

Aurel Holzschuh (University of Notre Dame, France) presented why malaria elimination is difficult in Zanzibar, an archipelago island with persistent malaria infections. Despite substantial reduction of *P. falciparum* in the last 15 years, progress towards elimination has plateaued. Aurel used high-throughput Multiplexed AmpSeq method to study the population structure and genetic differentiation within Zanzibar. Holzschuh results showed three problems illustrated below. They found that isolated populations could be targeted for elimination, that cases are in part fueled by household/village clustering and frequent travellers from mainland Tanzania facilitate *Plasmodium falciparum* continued transmission.



0410 - Deletions *Plasmodium falciparum* pfhrp2 and pfhrp3 Genes from Persons Presenting to Health Facilities in the Democratic Republic of the Congo, Ethiopia, Kenya, Madagascar and Rwanda, 2016-2018

Jessica McCaffery (Centre for Disease Control and Prevention - CDC, United States of America) examined how the deletions of *Plasmodium falciparum* histidine-rich proteins (pfhrp) 2 and 3 would compromise the validity of rapid diagnostic tests (RDTs) for people infected with *P. falciparum.* Jessica confirmed the presence of *pfhrp2*-deleted parasites in DRC, double *pfhrp2/3* deletions in Ethiopia and newly observed and reported pfhrp2 deletions in Madagascar. The *pfhrp2/3* deletions pose a threat to the validity of the HRP2/3-based RDTs which are widely used in sub-Saharan Africa to diagnose *Pf* malaria. Jessica aims to expand her investigations to include screening of pfhrp 2/3 gene deletions in other high malaria-burdened countries and recommends regular monitoring of *pfhrp* genes to ensure that RDTs are valid and reliable.

0853 - The importance of the Parasite Proteasome in Artemisinin Response

Melissa Rosenthal (University of Nebraska Medical Centre - UNMC, United States of America) looked into the effect of β2 parasite protein mutations on artemisinin-based combined therapies. The β2

mutants showed an increased sensitivity to malaria treatments (dihydroartemisinin and ozonide OZ439) in addition to increase in unfolded protein response activation and accumulation of K48-Ub (a polyubiquitin chain needed for protein degradation) in response to dihydroartemisinin. These proteins were associated with parasite death.

1049 - Quantification of the Sporozoite Inoculum from Mosquitoes with High and Low Salivary Gland Loads

Deborah Stiffler (Johns Hopkins Bloomberg School of Public Health, United States of America) highlighted the bottlenecks in malaria transmission and subsequently zoned in on quantifying sporozoite transmission from vector salivary glands to vertebrate hosts. Stiffler mentioned the difficulties of infecting mice with low sporozoite quantities which were one of the reasons why few sporozoite quantification experiments have been conducted. The next phase of this study will quantify the minimum threshold of sporozoites necessary for blood infection.

1165 - A Novel Physiological Model to Study *P. falciparum* Interactions in Placental Malaria

Rebecca Reif (University of Alberta, Canada) introduced us to a physiological assay that was used to assess the blocking efficiency of vaccine induced antibodies to prevent placental malaria. The study observed the *Plasmodium falciparum* protein VAR2CSA interactions with Chrondoitin Sulfate A in placental malaria. Rebecca's study is atypical as most placental malaria studies utilise a non-physiological assay; the gold standard. Physiological assays provide insight into how the vaccine-induced antibodies will work in humans. Rebecca concluded with an optimistic outlook despite the work that still needs to be done in regards to developing efficacious vaccine-induced antibodies that prevent placental malaria.

0457 - **Functional Genetics to Characterise *Plasmodium falciparum* acetyl-CoA Synthetase and discover Inhibitors**

Charisse Flerida Pasaje (Massachusetts Institute of Technology, USA) presented her work that aimed to characterise and to identify the functional potential of *Plasmodium falciparum* acetyl-coenzyme A synthetase, an enzyme, as a novel therapeutic target for malaria treatment. The enzyme was washighly potent and capable of abating parasitic growth in red blood cells. It, therefore, has been selected for drug development.

Plenary Session I: Opening Plenary Session

The virtual ASTMH 70th annual meeting was introduced by Christine Petersen (ASTMH Scientific Program Chair, United States). She warmly welcomed all attendees from over 100 countries. She commended the efforts of the chair of the program, 131 scientific program committee members and the ASTMH internal team for their expertise and commitments towards the annual meeting. Afterwards, a welcome remark was presented by Tedros Adhanom Ghebreyesus (World Health Organization - WHO, Switzerland) with emphasis on the emergence of Covid-19 and its adverse effects on human lives, society and disruption of disease programs as mortality increases, while treatments of NTDs, HIV/AIDs and malaria were stalled. Tedros Adhanom further discussed the approval and recommendation of WHO for broad uptake of the RTS,S malaria vaccine in addition to existing tools to save lives of children. He affirmed that WHO is making continued efforts to collaborate with countries and partners to make up for lost opportunities and to accelerate progress towards resilient health systems across the world.

The rewards to the malaria-related talks presented during the Young Investigator Awards were given to Melissa Rosenthal under the Winners category, Aurel Holzschuc and Geofrey Makenga under the First-Tier Mentions, and Isaac Namango, Charisse Flerida Pasaje and Felicia Watson under the Honorable Mentions category. Congratulations to all of you!

This report is brought to you by the MESA Correspondents Edima Ottoho, Tope Kayode, Franklin Tembongshu Formilack, Lucy W. Mwangi, Vita Mithi, Ana Alonso, Faith Hungwe, Olajoju Temidayo Soniran, Isabelle Delrieu, Doumbe Belisse Patricia and Carlos A. Fernández Miñope, with mentoring and editorial support from Divya Beri.

Day 2: 18th November 2021

Symposium #12: Entomological Data to Guide Strategic Deployment of New Types of Insecticide Treated Nets for Control of Pyrethroid Resistant Malaria Vectors

Amy Lynd (Liverpool School of Tropical Medicine, United Kingdom) started her presentation by giving background information on the importance of piperonyl butoxide-long lasting insecticide nets (PBO-LLIN) which combine pyrethroids with PBO. She provided an overview of the study which was a cluster randomised trial (CRT) conducted in Uganda following the nationwide distribution of LLINs with and without PBO. The primary outcome was to evaluate parasite prevalence by microscopy in children aged 2-10 years and secondary outcomes measured prevalence of molecular markers associated with insecticide resistance and LLIN coverage, survivorship, durability, bioefficacy and chemical content. Baseline survey showed that LLIN ownership and coverage had reduced markedly, parasitaemia and anaemia varied widely by region, and *Anopheles gambiae* s.s. was the predominant vector across all areas. At the end of the clinical trial, Lynd's group found that PBO-LLINs were significantly better at reducing parasitaemia and vector density than LLINs without PBO up to 25 months after distribution; decreased net coverage was associated with an increase in parasitaemia after 25 months; and housing type was an important risk factor for parasitaemia, vector density and net damage.

Joseph Chabi (U.S President's Malaria Initiative - PMI, VectorLink, United States) commenced his presentation by stating that malaria-endemic countries had distributed insecticide treated nets (ITNs) over the past two decades with little consideration to insecticide resistance monitoring data because the only available ITNs were pyrethroid-only nets. He also mentioned the pyrethroid resistance status across Africa which had led to the development of ITNs with combination of insecticides such as PBO synergist and chlorfenapyr. Hence, the U.S President's Malaria Initiative (PMI) VectorLink monitors resistance in focus countries with the vision to allocate resources appropriately to maximize impact of vector control tools. In these African countries, data on vector surveillance and resistance is collected from selected sentinel sites. Available data showed that PBO synergist and chlorfenapyr are effective at killing malaria vectors across PMI countries. In conclusion, he mentioned that several countries have introduced the use of new types of ITNs and PMI still follows up on durability monitoring of the ITNs

distributed across selected countries to continuously support and advise National Malaria Control Programs (NMCPs).

Ellie Sherard-Smith (Imperial College London, United Kingdom) presented a systematic review on an evidence-based framework to support selection of the most appropriate malaria vector control intervention in "location". The role of outdoor biting behaviours and residual transmission, IRS products, and mosquito net products in interrupting the transmission of malaria parasite was assessed using data from cluster-randomised control trials. Majority of the studied population stayed indoors and in bed at night. *Anopheles gambiae*, *An*, *arabiensis* and *An*. *funestus* were mostly active at night both indoors and outdoors. Residual transmission was geographically different with mosquitoes species having preferences to bite people, but this was not always related to human blood meals. However, mosquitoes were found to be resistant to insecticides and the entomological impact of mosquito nets showed that mosquitoes became more resistant to insecticides over time in Africa though the timing of the various trials differed and with varying seasons. The future perspective from the study is to use validated interventions in location-specific settings thereby reducing cost and increasing effectiveness of specific vector control mechanisms.

Constant Gbalegba (National Malaria Control Programme, Ivory Coast) presented entomological baseline data collected in 2019 on the new generation of ITNs that has been widely distributed in Ivory Coast between 2016-2020 with support of PMI VectorLink project. He discussed the various monitoring sites with indoor residual spray (IRS) and/or without IRS, insecticide resistance monitoring (IRM) sites and the entomological methods used in the study. With respect to insecticide resistance, he observed high pyrethroid resistance in all the monitored sites and PBO not restoring pyrethroid susceptibility. On the other hand, susceptibility to Chlorfenapyr, pirimiphos-methyl and Clothianidin varied across the sites. Vector human biting rates (HBRs) were high in Sakassou but low in Nassian, while infectivity and entomological inoculation rates also varied in the two study areas. These findings had implications for decision making for distribution of new generation ITNs and standard nets, and selection of IRS sites.

Symposium #15: Late-Breakers in Malaria

Both heme (a host-derived factor) and Histidine Rich Protein 2 (HRP2, a parasite-derived factor) released from lysed parasite erythrocytes contribute to human cerebral malaria (HCM) complications. **Adriana Harbuzariu** (Morehouse School of Medicine, United States of America) presented the results of an investigation into the pathways mediating heme and HRP-2-induced brain damage. She and her team showed that HRP2 reduced induced pluripotent stem cell (IPSC) proliferation and increased cellular apoptosis, necrosis and inflammation. Heme and HRP2 increased Toll-like receptors 1 and 2 (TLR 1 & 2) gene and protein expression in brain organoids, and monoclonal antibodies against TLR1 and TLR2 reduce the effects of heme and HRP2, thereby demonstrating a TLR1/2 dependent mechanism of action. The up-regulation of TLR2 expression by heme and HRP2 is also observed in the cortex of ECM (experimental cerebral malaria) mice and in the post-mortem brain cortex sections from HCM patients, suggesting that it may play an important role in scavenging of heme and HRP2 in the perivascular space as well as in malaria-induced brain inflammation. However, circulating Neuregulin-1 (NRG1; cytoprotective) declined in HCM, whereas tissue expression of NRG1 and its receptor ErbB4 in damaged brain areas were elevated. The findings show that heme and HRP2 effects are attenuated by exogenously augmenting the Neuregulin-1 a protective factor (NRG1). A very hopeful observation is that adjunctively administering NRG1 with Artemether in ECM mice eliminated parasite burden, reduced brain damage and ECM mortality.

The whole genome sequencing (WGS) of clinical isolates of *Plasmodium falciparum* is challenging due to low complexity sequences, multi-gene families, extensive nucleotide diversity, tandem repeats and

indels majority variation, as well as polyclonal infections and low parasitemia. **Karamoko Niare** (Brown University, United States of America) presented the development of a new variant calling pipeline for *Plasmodium falciparum* sequencing based on the Genome Analysis Toolkit (GATK). Firstly, parameters that control the heterozygosity, ploidy, assembly region and read quality were tuned. In addition, a high-quality training dataset was generated to filter false variants out. The GATK4-generated training Variant Call Format (VCF) shows high quality variants. When comparing the outputs to the gold-standard call-sets, the sensitivity of the new pipeline on simulated mixed infections is higher, reaching 71-84% for single nucleotide polymorphisms (SNPs) detection and 66-85% for indels in exons detection within the core genome. The sensitivity is higher than current pipelines for monoclonal infections, reaching 85-92% for SNPs and 88-90% for indels in the case of high-quality Illumina read data, and 78-80% for SNPs and 76-83% for indels in the case of low-quality reads. The precision for SNPS and indels is also higher than that observed for current pipelines: above 96% regardless of the read quality for SNPS, and between 93 and 95% on high quality reads and 76 to 93% on low-quality reads for indels. This new variant calling pipeline provides more accurate variant data. However, when applied to a large WGS dataset it can facilitate population genomics analysis that will serve as evaluation and identification of targeted interventions against the disease.

Resistance to first-line antimalarial piperaquine (PPQ) is observed in Southeast Asia and has been shown to be mediated by mutations in the drug efflux transporter PfCRT. **Laura Hagenah** (Columbia University in New York, United States of America) works with the team of David A. Fidock and they investigated whether the increasing usage of dihydroartemisinin-PPQ therapy in Africa could lead to the spread or the emergence of PPQ resistance in the continent. The most common chloroquine (CQ)-resistant *pfcrt* alleles in Africa were edited into the Dd2 *Plasmodium* parasite strain, and three PPQ-resistant PfCRT mutations seen in Southeast Asia were subsequently edited into these modified parasites. PPQ survival assays show that the F145I mutation in PfCRT confers high-grade PPQ resistance. The T93S mutation confers increased rates of survival at low concentrations of PPQ (~25 nM) in modified parasites. Resistance assays on other antimalarials and common combination therapy partner drugs were also presented. Results showed that PfCRT point mutations T93S, F145I, and I218F result in reduced degrees of resistance to CQ and its metabolite monodesethyl-chloroquine (md-CQ) on both GB4 and CAM783 haplotypes. The F145I mutation on GB4 PfCRT confers increased susceptibility to monodesethyl-amodiaquine (md-ADQ). These results suggest that increased dihydroartemisinin (DHA)-PPQ usage for seasonal malaria chemoprevention in Africa may result in PfCRT mutations that mediate resistance to PPQ.

Jack Hutter (Walter Reed Army Institute of Research in Silver Spring, United States of America) presented results from an expanded assessment of safety and immunogenicty of FMP014, a malaria vaccine candidate. FMP014 is composed of 60 monomers oligomerised into self-assembling protein nanoparticles (SAPN). Each monomer consists of CSP – representing the 3D7 strain of *Plasmodium falciparum* – that includes the C-terminus, 6 NANP repeats, and 2 CD4 viral epitopes. FMP014 is adjuvanted with the Army Liposomal Formulation containing QS-21 (ALFQ). Safety and immunogenicity were evaluated in ten U.S naïve adult subjects divided into 2 groups: group 1 receiving 20 µg FMP014 and 0.5 ml ALFQ, and group 2 receiving 40 µg FMP014 and 1.0 ml ALFQ, according to a 3-dose regimen (vaccinations: day 0, 28, and 56). Local solicited adverse events were mild and resolved within 72 hours. Systemic solicited adverse events were mild or absent in the low dose group and moderate in the high dose group. No related serious adverse events (SAEs) were observed. Assessment of serum antibodies by ELISAs to full length PfCSP, peptides containing (NANP) 6 and a C-terminal peptide, Pf16, both antibody titers and avidity indices increased after each dose. C-termiuns specific antibodies were dominant by a log over the anti-NANP response. A range of assays provided information on cellular responses induced by FMP014/ALFQ and specifically cytokine profiles, with IL-2 showing stronger response over IFN-gamma. There is a trend in favour of the lower dose administration to elicit an immune response, although the differences not significant. Although

not powered to yield associations with functional immunity, this study is the first demonstration of immune responses in subjects using targeted antigen display on the self-assembling protein nanoparticle vaccine platform.

Vaseline Stefanova (University Health Network and, Toronto General Hospital, Canada) presented the outcomes of research on a diagnostic marker for severe malaria in children. Malaria is the leading cause of childhood mortality in sub-Saharan Africa, with host immunity and endothelial activation contributing to the pathogenesis of the parasite. However, early symptoms are similar among febrile children, and current malaria diagnostic tools do not reliably identify children whose symptoms are caused by malaria. However, results of the prospective study of febrile children identified soluble urokinase-plasminogen activator receptor (suPAR) as a prognostic marker in Ugandan children at risk of severe malaria. Elevated levels of this marker were identified in critically ill patients as evidence of disease progression and poor prognostic index. This marker can further improve the prognostic accuracy of a validated clinical scoring system and suggest earlier application of malaria- specific treatment. This approach could decrease morbidity and mortality of malaria in children under 5 across the endemic regions.

Wes Boland (Indiana University School of Medicine, United States of America) discussed the implications of perfusion index (PI) as an indicator and prognostic marker for mortality in children with severe malaria. Malaria remains the leading cause of death among children under 5 with severe malaria about 67% mortality. PI is recognized as evidence of peripheral perfusion and circulatory status, therefore a decline in peripheral perfusion is indicative of impending circulatory shock with corresponding outcomes. Boland's study also found correlation between lower PI and the presence of subjective shock measures including capillary refill >sec, cold peripheries and lower limb temperature gradient. This finding suggests that PI could potentially be used as an alternative objective measure to diagnose shock in children with severe malaria. The findings also suggested the higher odds of in-hospital mortality with decreasing PI in cerebral malaria than severe malaria. These adverse outcomes are mostly seen in cerebral malaria cases. Therefore, efforts are being geared towards assessing the severity of malaria using pulse oximeter to measure the level of oxygen perfusion and assessment of shock.

Julie Wright (University of Toronto, Canada) presented the association of malaria in pregnancy (MIP) with intestinal permeability and preterm birth. Every year, 33 million pregnant women are at risk of malaria and the majority of these cases are in low-and middle-income countries. MIP is associated with adverse maternal and child outcomes including multi-organ failure, deaths and small for gestational age babies. The pathogenesis of this effect includes: sequestration of *Plasmodium falciparum* in the intestinal microvasculature; high grade parasitemia and bacteremia with corresponding metabolic acidosis observed in severe malaria as a result of the organic anions located within the gut. Similarly, severe malaria infection also induces low levels of bioavailable L- arginine resulting in increased gut leak which further worsens pregnancy outcomes. Wright's study hypothesized that disruption of intestinal barrier integrity and gut leak induced by MIP is associated with these adverse pregnancy outcomes, and bioavailable L-arginine in MIP is inversely associated with gut leak. The findings from this study suggest that MIP is associated with intestinal disruption and gut leak (measured using 2 different markers i.e. CD14 and LBP) leading to deficiency of L-arginine. These factors all increased the odds of preterm birth.

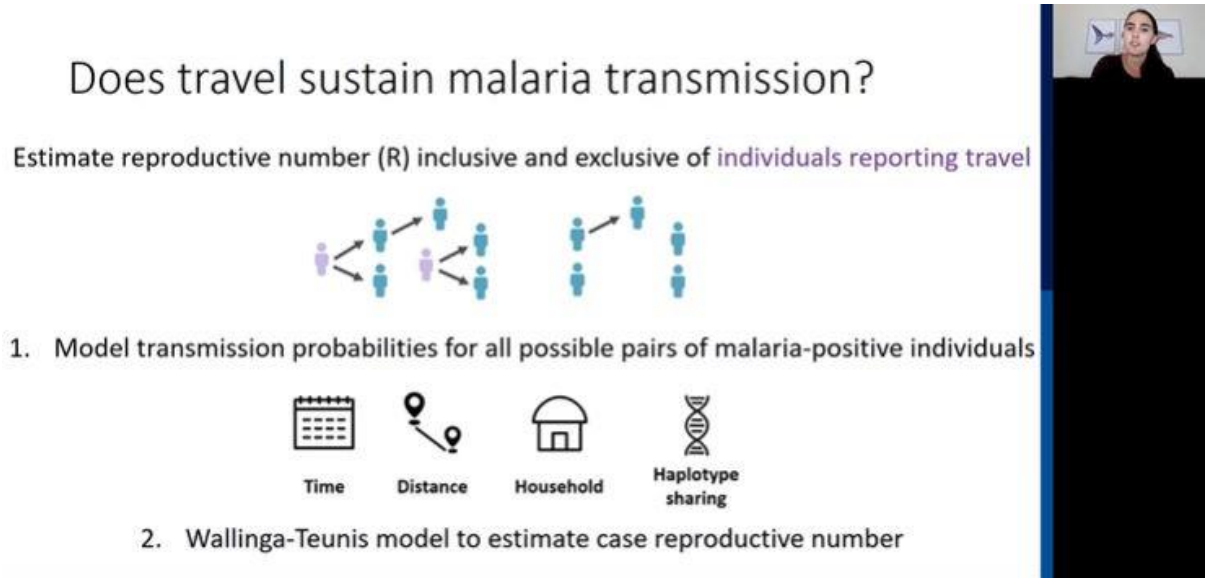
Symposium #19: Malaria: Epidemiology I - Surveillance Strategies

Arnau Pujol (Barcelona Institute for Global Health - ISGlobal, Spain) presented a study assessing the potential of pregnant women to reflect spatial and temporal patterns of malaria transmission in the community. Pujol compared polymerase chain reaction positivity rate (PR_{PCR}) from pregnant women

from the MiPMon project with PR_{PCR} from cross-sectional studies in children 2-10 years old. They also detected PR_{RDT} for pregnant women by defining a detection threshold, whereas results from PR_{RDT} for children were also available. They further evaluated the impact of different factors in pregnancy using subpopulations such as parity and HIV status. Both of these studies were conducted during the same time period in Manhica, Magude and Ilha Josina in Mozambique. The results showed strong correlation between PR_{PCR} from pregnant women and children 2-10 years regardless of HIV status or parity in all transmission settings. On the other hand, for PR_{RDT}, parity affected the linear regression slope i.e. lower with multigravid women and close to 1 for primigravid women. The study also revealed that temporal changes in PR from pregnant women were consistent with changes in incidence from health facility data with a time lag of 2 to 3 months.

Melissa Conrad (University of California, United States of America) discussed her study which showcased how school-aged children are the most important contributors to the human infectious reservoir for malaria in areas of high and low *P. falciparum* transmission intensity in Uganda. Children and adults were enrolled in cohorts in adjacent districts in eastern Uganda: Tororo district, where malaria transmission has diminished following effective vector control, and Busia district, where malaria transmission remains high. They quantified parasite carriage and contribution to transmission was measured via membrane feeding experiments in two settings of markedly different malaria transmission intensity in Uganda. Participants were recruited for passive and routine assessments. They found that despite marked differences in transmission intensity and clinical malaria incidence, children were responsible for most mosquito infection events in both settings. There was strong association between mosquito infection and gametocyte densities in both settings. They also found that asymptomatic infections were primarily the infection reservoir regardless of transmission intensity. She also mentioned that modeling work is ongoing to understand the contribution of age to the infection reservoir.

Christine Markwalter (Duke Global Health Institute, United States of America) discussed a study on malaria importation into an epidemic-prone setting in arid Northwest Kenya (Central Turkana). Here, *P. falciparum* events as well as its effect on local transmission was explored, and to achieve this, parasite collection was done in two groups - about 1,891 bus and plane passengers entering the region (active case detection) and from 1,891 RDT-positive index patients at 6 health facilities and 3,314 household members (re-active case detection). Subsequently, the parasites were genotyped using amplicon deep sequencing of *pfcsp* and *pfama1*, for which haplotypes were inferred using established methods. Results showed that *P. falciparum* qPCR positivity rate in inbound passengers was lower than in local household members. Overall, parasite importation by travelers into Central Turkana was detected; however, malaria is endemic and is sustained by local transmission. Therefore, interventions designed to suit the Turkana's unique ecology would help to drive down transmission.



Lek Dysoley (National Center for Parasitology Entomology and Malaria Control, Cambodia) discussed the impact of primaquine on *Plasmodium vivax* relapse among patients in Cambodia. He explained that Glucose-6-Phosphate Dehydrogenase (G6PD) testing to inform safe treatment with primaquine has been recommended by WHO to facilitate the safe use of primaquine to prevent relapses from dormant liver-stage *P. vivax* parasites. He described a phase 1 trial evaluating the impact of using G6PD RDTs and 14-day primaquine (PQ14) treatment as a radical cure on local *P. vivax* transmission. They analysed *P. vivax* cases, before and during the radical cure pilot to determine if their introduction caused a reduction in *P. vivax* and relapse cases. In total, 31,175 *P. vivax* records were used in relapse analysis, evenly distributed between radical cure and non-radical cure provinces. Results showed that *P. vivax* cases continued to decrease from about 3068 cases nationwide and 426 (14%) in radical cure pilot provinces in January 2018 to 423 nationwide cases with 110 (26%) cases in radical cure provinces in December 2020. He concluded that radical cure has proven to be a valuable intervention in the ongoing *P. vivax* elimination efforts in Cambodia and the Greater Mekong sub-region, as there is evidence of reduced relapse rates since its introduction in the 4 pilot provinces.

Jessica McCaffery (Centers for Disease Control and Prevention - CDC, United States of America) presented the results of the deletions of *P. falciparum* histidine rich protein (HRP) 2 and 3 genes from persons presenting at health facilities in the Democratic Republic of the Congo (DRC), Ethiopia, Kenya, Madagascar and Rwanda. They screened individuals enrolled in therapeutic efficacy studies of antimalarial treatments with a bead-based multiplex assay detecting HRP2 and pan-*Plasmodium* lactate dehydrogenase (LDH) and aldolase. Samples with low HRP2 signal relative to LDH or aldolase were then genotyped for *pfhrp2/3* deletions. They showed a sporadic and low prevalence of *pfhrp2/3* deletions from DRC, Ethiopia, Madagascar and Rwanda with no deletions observed in Kenya, demonstrating that RDTs based on only *pfhrp2* should still remain an effective testing strategy in these countries as the levels of *pfhrp2* and/or *pfhrp3* deletion exceeding 5% were not observed. McCaffery and her team recommend regular monitoring of the prevalence of *pfhrp2/3* deletions to ensure RDTs remain reliable.

Philipp Schwabl (Harvard University, United States of America) started his talk by justifying the purpose of their surveillance in Guyana. He explained that low transmission environments like Guyana are conducive to drug resistance emergence and a new mutation (Kelch13 C580Y) was observed in the last decade in Guyana that is resistant to artemisinin. His team applied a new multiplexed amplicon sequencing protocol for rapid molecular surveillance to monitor the persistence and possible expansion of C580Y-carrying parasites in >1000 *P. falciparum*-infected blood samples collected from

individuals in Guyana between 2010-2020. Furthermore, they intersected the amplicon sequencing results with 800+ whole-genome sequences from a 2016-2017 survey and found that various other clonal clusters occur between the two timepoints, suggesting that stochastic boom-bust dynamics can skew haplotype estimates inferred from cross-sectional sampling. Key takeaways were that amplicon multiplexes can cost-effectively extend/verify inference from whole-genome sequencing. Also, Kelch13 mutants are not expanding in Guyana like in Southeast Asia either because compensatory background is missing or broken apart by recombination. Transmission seemed not to be low/spatially restricted as to sustain clones with limited fitness advantage; and unstable genotype prevalence complicated cross-sectional interference. There are future plans to explore if they can reconcile observed rates of genetic change over 1.5 vs 4-year timescales with data on mixed infections and spatial gene flow/miner movement in Guyana.

Symposium #22: Malaria: Vaccines

RTS,S/AS01E has shown moderate vaccine efficacy when applied in African children using a scheme considering three primary doses at months (M) 0, 1 and 2, and then a delayed 4th dose given at M20; also, controlled human malaria infection studies in malaria naïve adults showed improved efficacy when a 3rd and/or 4th fractional dose was applied. With this context, **Aaron Samuels** (Centers for Disease Control and Prevention - CDC, Kenya) presented the results of the ongoing phase 2b open label randomized, controlled trial evaluating the efficacy of RTS,S/AS01E fractional dose (fx) regimens under conditions of natural exposure. Experimental regimens consisted of 2 full doses at M0 and M1 with either [i] full doses at M2 and M20 (R012-20), [ii] M2 and M14 (R012-14), [iii] Fx doses (1/5 of full dose) at M2 and M14 (Fx012-14), or [iv] at M7 and M20 (Fx017-20). 1500 Kenyan and Ghanaian children aged 5-17M were randomized (1:1:1:1:1) to receive RTS,S/AS01E (n=300/group) or a rabies control vaccine (n=300/group). All experimental regimens showed significant vaccine efficacy against the first episode of clinical malaria 12M post dose 3 and were well tolerated with no safety signals observed. Fx doses regimens did not show superior efficacy to full dose regimens; neither were they inferior. The vaccine efficacy obtained ranged from 35% (Fx012-14; 95%CI: 13-51%), to 47% (R012-14+R012-20; 95%CI: 31-59%), and 54% (Fx017-20; 95%CI: 38-66%). Trial is still ongoing as planned with continued follow-up until study end (M50).

From 2018, Hansenula polymorpha is used to produce R21, a construct with the circumsporozoite protein, fused to HBsAg. R21 is used with the Matrix-M™ adjuvant, a 40 nm lipidic complex, to form the R21/Matrix-M (R21/MM) malaria vaccine and **Mehreen Datoo** (University of Oxford, United Kingdom) presented its clinical development. R21/MM first showed high efficacy in phase I/IIa CHMI trials in naïve adults in the UK; a phase 1b age de-escalation trial in Kenya, showed good safety and immunogenicity in 91 adults, children and infants. A phase IIb field-efficacy study in 450 infants (5-17 months) in Burkina Faso administered three monthly doses prior to the malaria season. Efficacy of R21/MM with a high adjuvant dose for the first clinical malaria episode was 77%, while 76% for multiple episodes. A booster dose applied 12 months after first inoculation conducted to 81% and 77% efficacy for the first clinical episode and multiple episodes, respectively, after 24 months' follow-up. R21/MM had a favourable safety profile and high NANP specific IgG levels were observed, which correlated with vaccine efficacy. The highest levels of NANP specific IgG appeared 28 days after 3rd dose, and booster dose restored them to peak quantities. A phase III double-blind, randomised controlled trial has started across four African sites to test R21/MM at differing transmission patterns and malaria burdens, in a broader age-range of children. First results are expected in 2022.

The excitement produced by the use of mRNA as a platform for infectious disease vaccines in humans has been renewed given recent approvals and showed efficacy. **Evelina Angov** (Walter Reed Army Institute of Research, United States of America) replacing Ishita Waghela, presented the potential of an mRNA malaria vaccine based on the circumsporozoite protein of *Plasmodium falciparum* (*Pf*CSP).

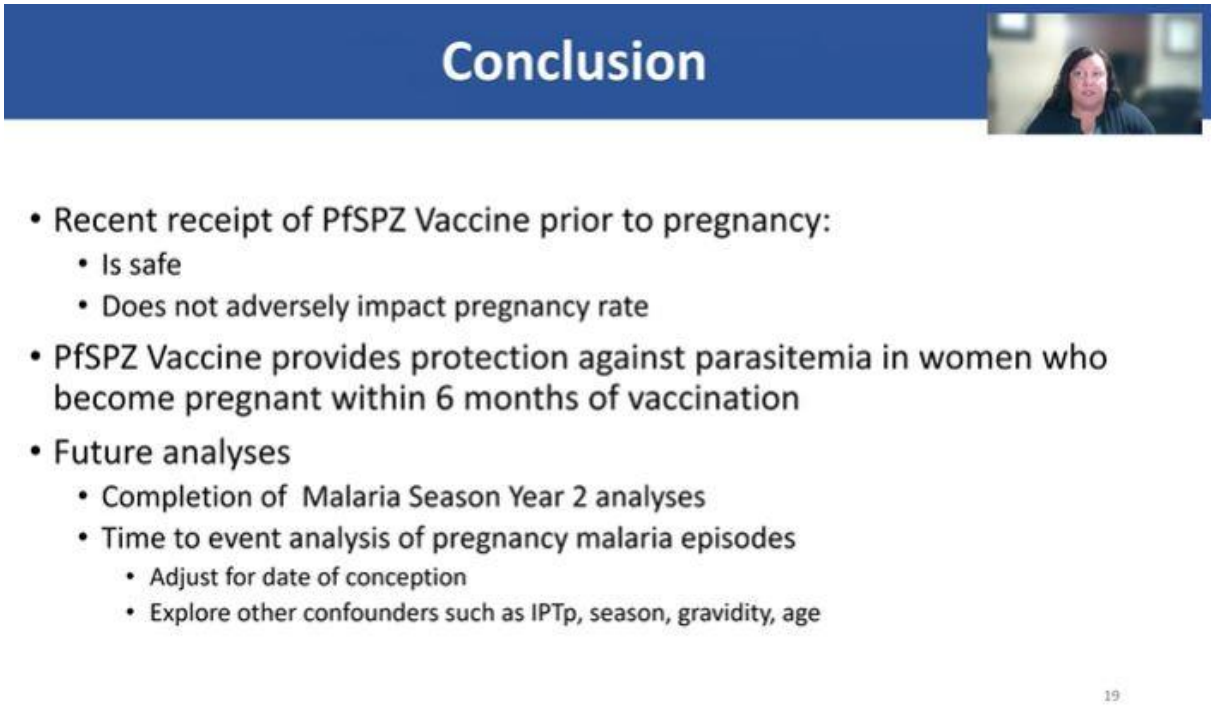
Immunogenic and protective potential of *Pf*CSP mRNAL-NP was assessed using an array of dosing factors including formulation, dose, interval, and number of immunizations. Experiments were carried out using two different mRNA transcript sequence elements (TriLink/unmodified and UPenn/nucleoside-modified) and were delivered using LNP1 lipid nanoparticle structure in two mouse strains (BALB/c and C57BL/6). The *in vitro* inhibition of liver stage development assay (ILSDA) was used to test the inhibition of sporozoites. Both *Pf*CSP mRNALNPs induced protective responses in mice. Low doses as 1μg induced durable antibody titers, and inhibitory antibodies produced by the UPenn/nucleoside-modified element were stable up to six weeks after final dose. Dose, schedule or mouse strain did not impact significatively the results. These findings call to consider the suitability of mRNA-LNPs for their use as vaccines in malaria.

Luna Barroco de Lacerda (Oswaldo Cruz Foundation Fiocruz-Minas, Brazil), discussed the designing of a malaria vaccine based on antigens presented by *P. vivax (Pv)*-infected reticulocytes. Many vaccines focus on the liver stage of the infection whose challenge is ability to activate antigen (Ag)-specific T cells or the blood stage of infection whose setback is that target antigen polymorphism requires high antibody titers. However, Barroco's group observed that cytotoxic CD8+ T cells recognize and kill *Pv*-infected reticulocytes. Fifty peptides were tested and 3 recombinant proteins (L30, S25, H2A) produced. Mice were immunized three times with each protein together with an adjuvant, followed by challenging with *P. yoelii (Py)*-infected reticulocytes. Findings indicate that 23 out of 50 peptides were immunogenic during the acute infection but 12 peptides remain immunogenic in the convalescent phase, suggesting an immunological memory. Additionally, *Pv* Ag-specific CD8+ T cells are shown to kill *Py*-infected reticulocytes, suggesting a cross-species protection. Lastly, L30 and S25 proteins can not only induce antigen-specific IgG1 and IgG2c responses, but also protective responses that resulted in the inhibition of up to 50-80% the parasitemia compared to the control group. Therefore, new *Pv* antigens were found to induce a protective response to *Py* infection, indicating cross-species protection and a potential vaccine candidate.

Issaka Sagara (University of Sciences Techniques and Technologies of Bamako - USTTB, Mali) presented findings of a phase 2 field trial of *Pfs*230D1-EPA/AS01E, a malaria Transmission Blocking Vaccine (TBV), in Mali, West Africa. Following an age de-escalation pilot study for safety (in 9-18 year olds followed by 5-8 year olds), a community based trial enrolled extended families as a unit (referred to as a vaccine unit [VU]) who were then vaccinated collectively on 0, 28, 56 days' schedule with either *Pfs*230D1-EPA/AS01E or comparator vaccine; children <5 years of age also were enrolled with their VU for parasitemia endpoints. All vaccinated individuals (5 years of age or older) were then followed post vaccination for safety, immunogenicity, and functional activity by standard membrane feeding assays (SMFA). School-aged children (9-18 year olds) underwent further assessment for functional activity by direct skin feeds (DSFs) every 2 weeks post the third vaccine dose for 8 DSFs and one year later, every 2 weeks post dose four for 10 DSFs with lab raised *Anopheles coluzzi* mosquitoes. No safety issues post vaccination or adverse events related to direct skin feeding (DSFs) were noted. *Pfs*230D1-EPA/AS01E showed an overall 73.6% efficacy against parasite transmission via DSF over two years combined; together justifying further studies as a viable malaria vaccine candidate alone or in combination with pre-erythrocytic vaccines.

Sara Healy (National Institute of Allergy and Infectious Diseases - NIAID, United States of America) in her talk emphasized the need to enhance protection against *Plasmodium falciparum (Pf)* infection in pregnant women and therefore reduce maternal, perinatal and infant mortality. Healy outlined successes of her group presented at previous meetings, including establishment of pregnancy registries at study sites as well as efficacy of 1-month PfSPZ Vaccine regimen and safety among women of childbearing potential. In a double-blind placebo controlled trial, Sanaria® PfSPZ Vaccine was administered to women of child bearing potential who planned to become pregnant during the study period but who also agreed to pregnancy prevention during vaccinations. The women were followed

for approximately 1.5 years post enrollment for pregnancy. Pregnant women, and their offspring, underwent exploratory analysis for safety and parasitemia. Results indicated that recent receipt of PfSPZ Vaccine prior to pregnancy is safe and does not adversely impact pregnancy rate. Further, the study showed that PfSPZ Vaccine provides protection against parasitaemia in women who become pregnant within 6 months of vaccination. Future analyses will adjust for date of conception, IPTp dosing, prior parasitaemia, gravidity, seasonal variation of the parasite as well as immune responses against infection to fully elucidate durability of protection and fully characterize receipt of PfSPZ Vaccine in women who become pregnant shortly after vaccination and supports future studies in pregnant women.



Felicia Watson (University of Washington, United States of America) representing her group discussed considerations to translate the 'Prime-and-Trap' malaria vaccine strategy targeting the pre-erythrocytic stage of infection to the clinic. Prime-and-Trap entails the trapping of *P. yoelii* circumsporozoite (*Py*CSP)-specific CD8+ T cells elicited by DNA priming into the liver by giving a booster with liver-homing radiation attenuated sporozoite (RAS). Although Prime-and-Trap confers durable protection in a rodent malaria model, the requirement for high doses of IV administered RAS is a potential impediment for translation to larger animal models or humans. Therefore, this group analysed whether translational potential to clinic could be improved by reducing the RAS dose, eliminating IV RAS administration, and adding a glycolipid adjuvant, 7DW8-5. They observed that the efficacy of Prime-and-Trap with IV RAS administration is durable with or without the adjuvant for at least four months; co-administration of RAS+7DW8-5 confers protection in mice models with a 4-fold lower dose, and intradermal delivered RAS+7DW8-5 confers protection after Prime-and-Trap. In conclusion, Felicia stated that Prime-and-Trap is a promising and translatable vaccine strategy, co-administration with a glycolipid-adjuvant is dose sparing and improves efficacy with intradermal *Py* RAS delivery.

Symposium #27: Expanding the Use of Radical Cure to Patients with Uncomplicated Malaria Due to Any Plasmodia Species

Robert Commons (Menzies School of Health Research, Australia) began by reminding us that *Plasmodium vivax* (*Pv*) is now the predominant species of malaria in Asia and the Americas. He

stressed the importance of improving the radical cure of *P. vivax* to kill hypnozoites, the silent reservoir of infection in a human host. He presented results from an individual patient pooled meta-analysis defining the risk of *Pv* parasitemia after *P. falciparum* (*Pf*) infection. The biggest cause of recurrent malaria by day 63 was due to *Pv* rather than *Pf*, and this was particularly apparent after ACTs with short half-lives such as artemether-lumefantrine. The risk of *Pv* was also greater in areas of high relapse periodicity, in children, and in patients who cleared their initial parasite clearance slowly. The latter suggests that *Pv* reactivation might be triggered by symptomatic *Pf* malaria. In conclusion, in some co-endemic areas there is a high risk of *Pv* after *Pf* infection, suggesting potential benefit of treating all patients with uncomplicated malaria with ACT plus primaquine.

Jeanne Rini Poespoprodjo (Gadjah Mada University, Indonesia) presented a cluster randomised study of supervised versus unsupervised primaquine for the treatment of *Pf or Pv* malaria in Papua, Indonesia. In malaria endemic countries many patients do not complete the 14 day PQ recommended regimen and this leads to poor adherence and antirelapse effectiveness. In the Indonesia trial, 223 patients were randomised to a 14-day regimen of primaquine (total dose 7mg/kg), which was supervised on alternate days, and in the other arm, 196 patients received unsupervised primaquine. The clusters were selected according to location, size and annual parasite incidence. The results showed that at 6 months follow up, partial supervision of 14-days primaquine significantly reduced the risk of recurrent *Pv* by 77% and the rate by 37%. Importantly the benefit of partial supervision was apparent in patients presenting with *Pf* malaria, reducing *Pv* recurrence by 48%, supporting the idea that universal radical cure in areas with a high risk of *Pv* and *Pf* might work be implemented. Alternate day supervision may not be feasible so now studies are underway to find ways of improving adherence with fewer follow up visits.

James Walker (University of Melbourne, Australia) presented a malaria model to compare treatment for multispecies infections (A multispecies malaria model). The aim was to develop a model that could compare both *Pv* and *Pf* dynamics and the interactions between those in an individual host. This would allow for scenario modelling of different treatment strategies. His presentation focused on the universal radical cure scenario, using casework load data from Cambodia to validate his model. The scenario analysis showed that implementing a unified treatment policy of ACT plus 14 day primaquine for patients presenting with uncomplicated malaria due to any species, lead to significantly fewer infections and deaths in the population over a ten-year period. James ended by suggesting that future work should be done in the form of sensitivity analysis, since many of the parameter estimates in the model may differ significantly in different endemic settings.

Angela Devine (University of Melbourne, Australia) introduced her talk on the cost-effectiveness of universal primaquine radical care policy by highlighting some of the benefits of universal radical cure, which included accurate diagnosis, and ensuring that all patients get effective treatment for the particular malaria species they are infected with. Angela reminded us that misdiagnosis of *Pf* malaria as *Pv*, resulted in results in patients being treated with chloroquine that could result in recurrent infection and even death. Pragmatic benefits of a universal approach include simplified patient flow for health workers and fewer drugs to keep in stock. Using data derived from the model that James Walker presented, she conducted an exploratory cost-effectiveness analysis for Indonesia, for implementation of ACT plus 14 days primaquine active against all l species of human malaria. In view of the risk of PQ induced haemolysis, all patients were tested for G6PD-deficiency before prescribing PQ, and this incurred additional costs. However, her analysis showed that universal radical cure policy can avert a large number of cases, at a cost of $112 per case of malaria averted. In a sensitivity analysis on G6PD test cost and the results showed potential to become cost-saving in high burden areas, decreasing the costs to $35 per case averted. In summary, a universal radical cure for malaria has many potential operational and economic benefits to reduce the burden of malaria.

Symposium #28: Early Experience and Next Steps in the Evaluation of the Attractive Targeted Sugar Bait for Malaria Control in Kenya, Mali and Zambia

Helen Jamet's (Bill & Melinda Gates Foundation - BMGF, United States of America) presentation gave us a detailed overview on the development of attractive targeted sugar baits (ATSB) and the research that is being done towards introducing ATSB as a new malaria prevention method. She explained that vector control tools must seamlessly integrate into daily life and that novel control methods must exploit mosquito behavioural patterns like ATSB does. ATSB exploits mosquito feeding behaviours by using a sugary syrup mixed with a toxicant to attract and upon ingestion, kill mosquitoes. Westham Co. developed an ATSB prototype whose proof-of-concept was observed in Mali in 2017. This became fundamental for data collation of product organisation and testing and entomological validation in Mali, Zambia and Kenya. The data obtained from this research will be used to demonstrate the public health value of ATSB. However, before public health value can be demonstrated, lab and field work are still critical to optimise product specifications, to determine product cost-effectiveness as well as ensuring WHO approval prior to ATSB's commercial use. Jamet concluded her talk with enthusiasm towards the influential impact that ATSB will have on the vector control landscape if it becomes successful.

Eric Ochomo (Kenya Medical Research Institute - KEMRI, Kenya) stated that mosquito feeding rates on attractive sugar bait without toxin (ASB) established in Mali demonstrated the effects of ATSB on mosquito populations. From these research trials, it was found that daily feeding rates were similar between 2 and 3 ASB stations whilst a modelling frame suggested that a feeding rate of 2.5% is necessary to reduce malaria incidence by 30% in 2 years. This study, conducted in Zambia and Kenya, aimed to determine feeding rates of *Anopheles funestus* and *A. gambiae* and to assess the temporal distribution of feeding rates. The results showed that *A. funestus* feeding rates (in Kenya and Zambia) surpassed the 2.5% modelling threshold whilst *A. gambiae*'s feeding rates in Kenya did not surpass this threshold OR while the same did not hold true for *A. gambiae*'s feeding rate in Kenya. No significant difference was found in the number of ASB stations used in both countries suggesting that the same would apply to ATSB stations. A significant difference was observed in feeding rates between *A. funestus* and *A. gambiae* in both Kenya and Zambia with *A. funestus,* the primary vector, having a higher feeding rate than *A. gambiae*. The results imply that ATSB would be very effective against *A. funestus,* especially during the rainy season when increased feeding rates were observed. Increased feeding rates do not, however, affect the efficacy of ATSBs.

Kafula Silumbe (PATH, Zambia) stated that ATSB is a promising new vector control tool, however, community engagement (CE) is vital for its success. He conducted a randomized control efficacy trial to demonstrate ATSB's potential public health importance via CE strategies. These aimed to support high intervention coverage and foster participation in trial study components that will form guidelines for future ATSB field trials. Challenges faced during the trial were widespread rejection of the intervention due to inadequate information or poor perception of ATSB by the local community. The importance of using CE strategies was highlighted during community meetings or consent and installation processes where ATSB knowledge was garnered by community members. The CE approaches implemented were ensuring a dedicated budget with project staff to develop, implement and monitor activities as well as training community members to lead sensitization efforts, retrieve and share community feedback routinely with the study team. Furthermore, health staff had to be engaged to readily handle severe adverse events. Silumbe emphasised the importance of having a feedback loop between community members and study liaisons to identify and rapidly resolve any concerns or questions and concluded that crisis communication plans are vital for guiding rapid responses to unanticipated events.

Potential Threats/Challenges to the Trial

1. **Moderate to widespread rejection of the intervention in one or more study clusters.**
   - Perceptions, beliefs, and/or inadequate information about ATSBs may lead to refusals during initial product installation and/or removal or tampering with the product.

2. **Moderate to widespread refusal to participate in one or more study components.**
   - Trial includes blood testing for malaria.
   - 2 year trial, participation fatigue may set in for some study components.
   - Maintaining participation may be particularly challenging in control areas.

Mohamed Traore (University of Science and Technology of Bamako, Mali) presented findings from an entomological field study conducted in Northern Mali in 2019 to explore the potential of ATSB in a low-endemicity setting, with the primary vector being *An. gambiae s.I*. He explained that a pre-post study design was used, in which ten villages received 5,677 ATSBs (2 ATSBs per eligible structure) and another ten villages served as the control group with no ATSBs. The ATSB installation period was from July until September and stations were removed in late December of the same year. Entomological measurement was conducted monthly with mosquitoes being collected using CDC-UV traps, pyrethrum spray catch, and indoor and outdoor human landing catches. A mixed methods approach was used to process the mosquitoes. This included ovariole dissection and gonotrophic cycles quantification, ELISA to detect sporozoites and PCR for species identification. The result of comparison between ATSB intervention and control villages showed lower female *An*. *gambiae s.I*. abundance with lower proportions that were positive for malaria sporozoites (near zero) and with ≥ three gonotrophic cycles in the test group. These observations suggest that ATSBs have the potential to make a significant impact on malaria transmission in areas of low transmission.

Symposium #33: Towards a Next-Generation Malaria Vaccine Portfolio: Innovations in Malaria Vaccine Development

B. Kim Lee Sim (Sanaria Inc., United States of America) started her presentation sharing WHO's hopes of 'eventually having a vaccine that is 95% effective and can essentially eradicate malaria'. Then she highlighted the primary goal of Sanaria as to develop and commercialise a vaccine that is well tolerated and safe and can be used as a tool for malaria elimination. They have developed *Plasmodium falciparum* (*Pf*) sporozoite (SPZ) vaccines using aseptic, purified, live, attenuated vialed cryopreserved *PfSPZ* that meet regulatory standards. She discussed the *Pf* development in the liver and the importance of *PfSPZ* vaccines on the prevention of homologous and heterologous controlled human malaria infection (CHMI) with *Pf* parasites. In order to achieve their aim, Sanaria is focusing on four major research areas which include: (i) to receive marketing authorization and initiate commercialization for the radiation-attenuated *PfSPZ* vaccine, (ii) to reduce costs of goods by 75% to 80% by increasing potency, (iii) to reduce costs of goods by 80% to 90% and further increase consistency and reproducibility of manufacturing, and (iv) to use a *PfSPZ* vaccine as the lead agent in malaria elimination campaigns, currently focusing on supporting Equatorial Guinea and Tanzania. She explained their evidence-driven strategies to achieve these plans, as well as ongoing and planned clinical trials. She mentioned that the first *PfSPZ* vaccine for *Pf* malaria prophylaxis will move to

marketing authorization in 2023. Additionally, their discovery of a hollow fiber culture system for mass production of *in vitro* PfSPZ will reduce the cost of producing vaccines.

Simon Draper (University of Oxford, United Kingdom) commenced by presenting on the challenges facing development of blood stage malaria vaccines which includes (i) antigenic polymorphism and redundant invasion pathways of leading antigen targets; (ii) lack of *in vitro* correlate of *in vivo* protection; and (iii) the need to induce an extremely high antibody concentration for protection, and to maintain this for a useful duration of immunity. He discussed extensively studies that highlighted the rapid progress made on the development of next-generation blood-stage vaccines for both *Pf* and *Plasmodium vivax* (*Pv).* This progress has been enabled by improved essential or conserved target antigens, improved tools to measure antibody structure-function relationships, and optimized delivery (quantity, quality and longevity) of vaccine-induced antibody responses.

Hernando del Portillo (Barcelona Institute for Global Health & Germans Trias i Pujol Research Institute, Spain) discussed *Plasmodium vivax* infection, which accounts for 2.5 billion people at risk and up to 7.5 million clinical cases. The parasite is endemic in Latin America and Asia. *P. vivax* is resistant to elimination - about 70% of infections are asymptomatic and poses a challenge for control of infection when compared to *P. falciparum*. More so, recent clinical data suggest that *P. vivax* causes cryptic erythrocytic infections with spleen and bone marrow invasion, different from *P. falciparum* infection which is mostly in the circulatory peripheral blood. The pathogenesis makes the elimination of *P. vivax* more demanding, and *P. vivax* cannot be controlled or eliminated if we depend on the present tools being used to combat *P. falciparum* infection. Therefore, we need new tools such as the novel discovery of reticulocyte-derived exosomes as a new antigen for vaccine development against *P. vivax* malaria.

Ashley Birkett (PATH, United States of America) presented lessons learnt from the Covid-19 pandemic to inform the development of malaria vaccines. This was premised on sharing contrasting views with respect to research and development (R&D) and investment opportunities between Covid-19 vaccine and the new malaria vaccine. Although both infections are of global health emergency, the process of development of the Covid-19 vaccine was facilitated within a year compared to the WHO approved RTS,S malaria vaccine that took years. The biological differences posed by malaria, long follow-up time, and funding gaps were some of the challenges identified. However, the Covid-19 vaccine received $5.5 billion funding support for R&D within the first 12 months, while all malaria R&D had an annual investment of $600-700 million, of which the vaccine R&D had a share of about $130 million. Additional support of $600 was received from partners and countries for scale-up of Covid-19 vaccine; being some examples of the game change witnessed in the Covid-19 vaccine production. Similarly, new malaria R&D opportunities such as the mRNA vaccine and investment in African manufacturing companies were discussed.

Symposium #35: Community Delivery of Intermittent Preventive Treatment (IPTp): How It Contributes to the Goal of Improved Maternal and Newborn Health Outcomes

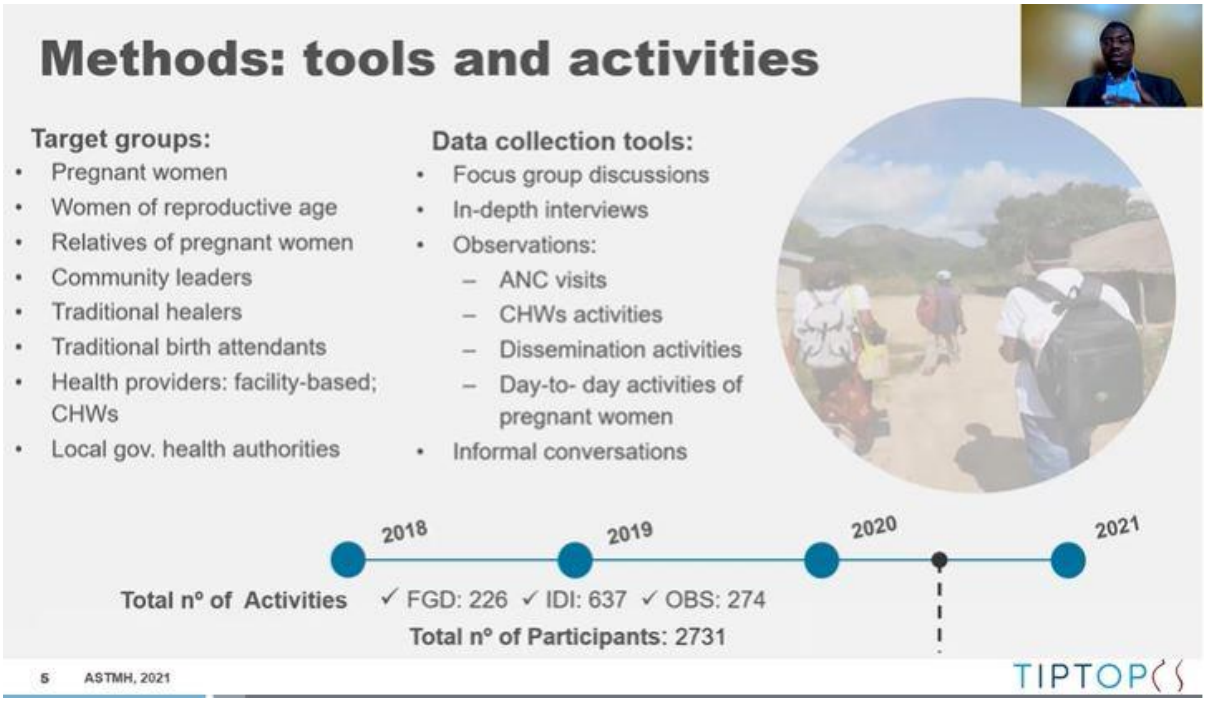
Introductory remarks by **Pedro L. Alonso** (WHO Global Malaria Programme, Switzerland) emphasized the importance of preventing malaria in pregnant women so as to eliminate adverse events associated with malaria in pregnancy such as maternal mortality, anaemia, low birth weight, and infant mortality. He pointed out that tools against malaria prevention are not perfect alone and there should also be concerted efforts in timely testing, diagnosis and treatment of malaria. Alonso further emphasised that antenatal clinic (ANC) visits are crucial to reducing missed opportunities for diagnosis and treatment. He lauded the steady increase in overall IPTp coverage from 2% to 34% over the last 10 years but noted the unacceptably low coverage in pregnant women. Alonso in conclusion encouraged

development of projects which explore community-based approaches to complement existing measures to increase IPTp access; making a call to action to protect pregnant women.

Odete Cossa (Jhpiego, Mozambique) introduced the 5 year Transforming Intermittent Preventive Treatment for Optimal Pregnancy (TIPTOP) project rolled out in Mozambique, Democratic Republic of Congo (DRC), Nigeria and Madagascar with the aim to reduce maternal and neonatal mortality by expanding access to quality-assured sulfadoxine-pyrimethamine (SP) for IPTp. TIPTOP has seen increased uptake of three doses of IPTp without decreasing antenatal clinic (ANC) attendance by achieving three goals. First, implementing community based IPTp-SP by ensuring strong partnerships with stakeholders; strengthening existing health systems; capacity building of health care providers, maintaining engaged communities; deploying trained community health workers (CHWs) to screen pregnant women and provide SP by directly observed therapy (DOT); and generating evidence to inform policy decisions. Second, improving supply of quality-assured SP. And third, by establishing support for transition, scale-up and sustainability of community delivery IPTp-SP (C-IPTp-SP) by the ministries of health in the four countries. Cossa noted that like many health projects, TIPTOP was impacted by COVID-19, however they sustained community essential services, and ensured protection of health workers and clients. Then she emphasized that success has to be grounded on engagement with community civil organisations and community leaders through government-led partnerships. She concluded by stating that community engagement ensures creativity, innovation and adaptability, all key elements for short and long term gains for prevention of malaria in pregnancy.

Herbert Onuoha (Jhpiego, Nigeria), working with the TIPTOP project also emphasized that robust health systems management information (HMIS) and engagement of Ministries of Health (MOH) are keys to successful project implementation. Rapid facility assessments (RFAs) revealed varied gaps across all the countries related to the HMIS system and its utilization that was tackled by using a targeted approach. New data elements were added in HMIS for IPTp reporting and C-IPTp was integrated into an existing data flow. Stakeholder-led partnerships were key to ensure coordination, sharing and planning within TIPTOP, which also employed mobile data collection and reporting for C-IPTp data which ensured timeliness. However, some challenges such as increased requirements for smart-phones and data connectivity were observed. Onuoha concluded by pointing out that engaging MOH and other stakeholders ensured effective C-IPTp implementation and monitoring; strengthening existing HMIS to include data from private sectors and the community drove programmatic and technical quality for sustainability, and finally that regular supportive supervision and positive feedback motivates service providers for improved service and data quality.

Ogonna Nwankwo (University of Calabar, Nigeria) presented the preliminary findings from a qualitative study that assessed the acceptability of C-IPTp and barriers and opportunities for C-IPTp uptake and antenatal care (ANC) attendance in the TIPTOP implemented countries. Overall, C-IPTp has been widely accepted by its beneficiaries in all project areas. However, community health workers' (CHWs) workload and lack of incentives were identified as a barrier to C-IPTp. Health seeking barriers identified were perceived fear of sulfadoxine-pyrimethamine (SP) side effects, women's lack of autonomy, and impaired access to health facilities due to financial and logistical constraints. Likewise, health-seeking facilitators identified by this study include trust in SP efficacy, awareness of malaria symptoms and severity, general acceptance of medical pluralism, involvement of relevant community stakeholders in dissemination of information, trust and acceptability of CHW and awareness of SP and ANC as important preventive measures. Ogonna concluded on the importance of addressing beneficiaries and CHWs concerns over C-IPTp delivery to reduce maternal and neonatal mortality due to malaria. He further emphasized replanning sensitization strategies that can address context-specific barriers.



Clara Menéndez (Institute of Global Health in Barcelona - ISGlobal, Spain) presented preliminary results from household surveys on key indicators including coverage of at least 3 courses of IPTp (IPTp 3+) and attendance to antenatal care clinics from 2018 to 2019/20. IPTp3+ coverage was much higher after one year of TIPTOP project implementation than at baseline for DRC, Nigeria and Madagascar, except Mozambique where the coverage decreased. Four those 3 countries the average number of courses per woman is more than 3. Attendance in ANC4+, ANC1+ or early ANC attendance remained stable or decreased during the period. Menéndez then presented an estimation of the effect of community IPTp (C-IPTp) on IPTP 3+ coverage using a difference-in-differences (DiD) method. This method allows to compare over time before-after changes in the intervention population with the before-after changes in a control population and to adjust for potential confounders. It shows that C-IPTp may have contributed to the increase in IPTp3+ coverage in all countries but Madagascar. Contextual factors such as dramatic meteorological events, insecurity and political changes as well as COVID-19 restrictions affected negatively both ANC attendance and IPTp3+ coverage in Mozambique.

Symposium #43: Clinical Development of Malaria Transmission Blocking Vaccines: Which Road Do We Take?

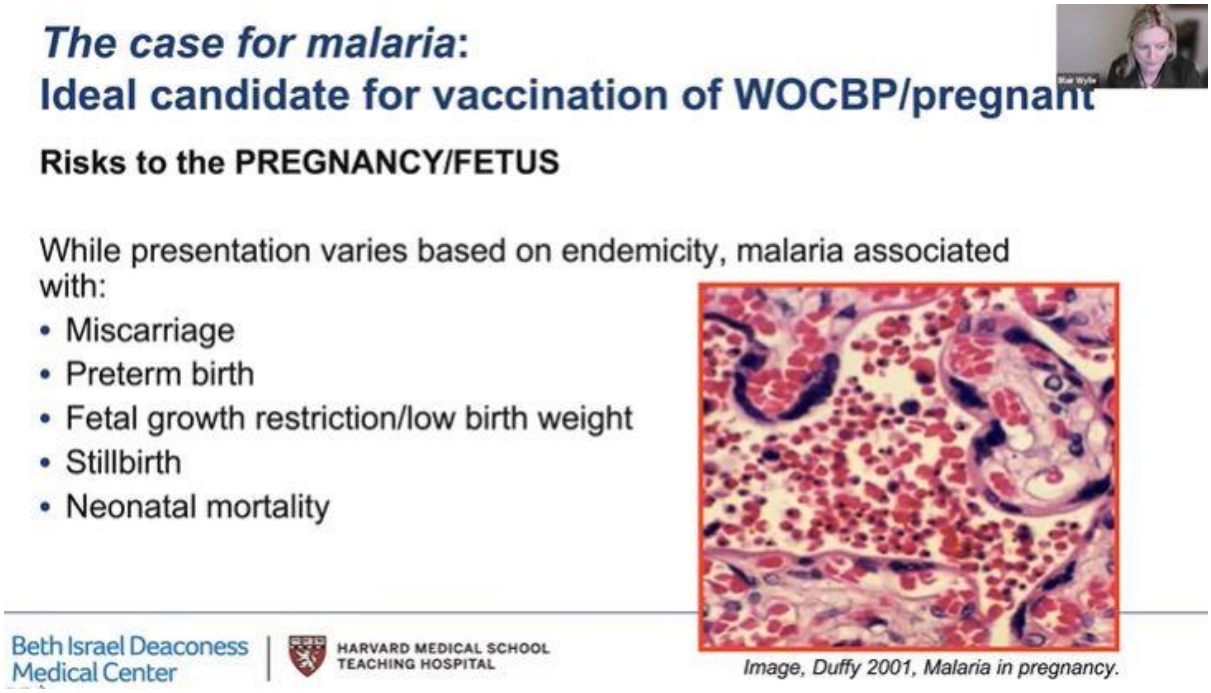
** Not yet available.*

This report is brought to you by the MESA Correspondents Edima Ottoho, Tope Kayode, Franklin Tembongshu Formilack, Lucy W. Mwangi, Vita Mithi, Ana Alonso, Faith Hungwe, Olajoju Temidayo Soniran, Isabelle Delrieu, Doumbe Belisse Patricia and Carlos A. Fernández Miñope, with mentoring and editorial support from Divya Beri.

Day 3: 19th November 2021

Symposium #52: Trials of Malaria Vaccines in Pregnant Women

Blair Wylie (Beth Israel Deaconess Medical Center, United States of America) started her presentation with a keen look at the impact of COVID19 in pregnancy which has a higher risk of complications and death among pregnant individuals. Even though preliminary data on mRNA vaccines in pregnancy showed a very similar side effect profile to that in the general population, vaccine coverage in pregnancy in the USA is still very low < 30%. This can be attributed to a number of reasons. Pregnant women have historically been excluded from participation in clinical trials, after some drug interventions famously caused harmful sequelae during pregnancy ex. thalidomide and diethylstilbestrol. However, when women are excluded from trials, safety data must then be gathered post-licensure during routine use rather than from randomized control trials, leaving the perception that vaccination during pregnancy may be unsafe, and consequently putting more women at risk of harm. Wylie then pivoted to malaria vaccines during pregnancy, an ideal indication for vaccination especially with the heavy burden of adverse outcomes associated with maternal malaria for the mother and the fetus. She concluded by emphasizing that complications occur in pregnancy and these vary by gestational age, therefore these baseline complication rates need to be taken into consideration when designing a clinical trial in pregnancy so as to not over-ascribe harm to the intervention (e.g., vaccine).



Image, Duffy 2001, Malaria in pregnancy.

Michal Fried (National Institute of Allergy and Infectious Diseases - NIAID, United States of America) described the role of a pregnancy registry to prepare for a vaccine trial in pregnant women. She first described a longitudinal cohort study in Ouelessebougou, Mali, that highlights the urgent need for a malaria vaccine for pregnant women: of the 1850 women enrolled, about 70% of women harbored the malaria parasite at least once during the pregnancy with the majority diagnosed at enrolment. Malaria infection during pregnancy increased the risk of stillbirth and preterm delivery in primigravidae and the risk of early neonatal death in multigravidae. Subsequently, a pregnancy registry study was conducted to collect baseline information on pregnancy outcomes and involved two cohorts. In the first cohort enrolled during antenatal clinic visits (ANC), the largest proportion of the 1814 pregnant women enrolled were aged 20-35 years, multigravid, used insecticide treated nets

(ITNs), received 1-2 courses of intermittent presumptive treatment in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP), and first attended ANC during their second trimester. Maternal factors associated with perinatal death were primigravida and age <20 years. Odds of low birth weight (LBW) were higher in primigravidae and women aged <20 years. In the second cohort of women of childbearing age who were enrolled before conception, 799 non-pregnant women were followed for 2 years to observe early pregnancy and its outcome. Preliminary data analysis of 357 pregnancies revealed that the largest proportion of women were multigravidae aged 20-25 years; miscarriage was the most common adverse outcome. Primigravidity and malaria infection were independently associated with preterm deliveries. This background information on poor pregnancy outcomes and risk factors is the key to design and monitor future interventional trials in pregnant women.

Halimatou Diawara (University of Sciences, Techniques and Technologies of Bamako - USTTB, Mali) began her talk by reiterating that malaria is indeed a huge public health challenge especially among pregnant women; statistics show that about 11 million pregnant women in sub-Saharan Africa are infected with malaria annually. She further emphasized that there is an urgent need for new tools to control malaria during pregnancy. Diawara went on to describe trials conducted in Ouelessebougou, Mali, using Sanaria, Inc. PfSPZ Vaccine candidate, in order to prepare for future trials in pregnant women. PfSPZ has previously been found to be efficacious for preventing infection in healthy malaria-exposed adults. The group observed that a short 4-week PfSPZ Vaccine regimen is safe among women of childbearing potential (WOCBP) and confers significant efficacy against *Plasmodium falciparum* infection and, for the first time, against clinical malaria episodes. Also for the first time, the team observed that the efficacy of PfSPZ Vaccine persisted for two years, against both *P. falciparum* infection and clinical malaria. The team concluded that the short 4-week vaccine regimen will be appropriate to test in pregnant women and that presumptive antimalarial treatment before immunization seems to be a requirement for PfSPZ Vaccine field efficacy.

Morten Nielsen (University of Copenhagen, Denmark) discussed his ongoing work to optimize vaccines based on the VAR2CSA protein that the parasite uses to bind and sequester in the human placenta. He suggested that the target product profile of the vaccine would require two doses, could be administered prior to pregnancy, and would target the majority of VAR2CSA genotypes. In phase 1a/b trials, two VAR2CSA vaccine candidates (PAMVAC and PRIMVAC) were safe and well tolerated, immunogenic, generated antibodies reacting with homologous VAR2CSA-expressing parasites, and induced functionally active antibodies. Further studies are ongoing to determine the longevity of the immune response, the capacity to be boosted by natural exposure, and cross-reactivity of vaccine-induced immune responses. His team is now analysing CLP-based PAMVAC and multi-PAMVAC nanoparticle vaccines. The platform used for the vaccine is simple, versatile and universal to create capsid virus-like particles (cVLP) for any antigen. Lessons from the recent scale up of the COVID-19 vaccine as well as the vaccine against *human papillomavirus* supports the manufacturability of such cVLP-based vaccines. Nielsen concluded that novel vaccines or novel modes of administration of vaccines are needed for malaria vaccine development; and that a combination of vaccines targeting different parasite stages may lead to greater efficacy.

Symposium #57: Alan J. Magill Malaria Eradication - Keeping Malaria Eliminations on Track (The Successes and Challenges on the Pathway to Eradication)

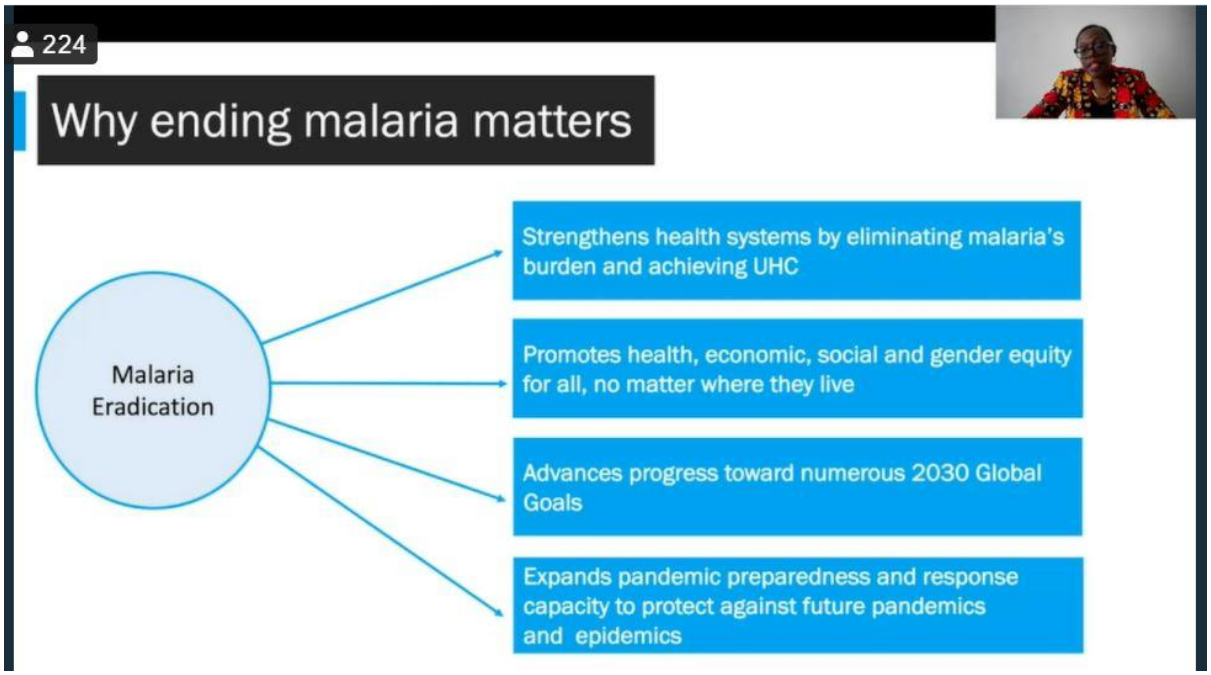
The symposium began by paying tribute to Alan J. Magill, the former ASTMH president and congratulating Tshokey Tschokey (Bhutan); the 5th Magill Fellow (2021).

María Eugenia Grillet (Central University of Venezuela, Venezuela) started her presentation with an overview of malaria morbidity and mortality in the Americas during the past decade, and the major cause of malaria being *Plasmodium vivax* (76%) followed by *Plasmodium falciparum* (24%). She

mentioned examples of E-2020 countries that are certified malaria-free and lessons that can be learned from them which includes political commitment, strong surveillance system, prompt diagnosis, appropriate treatment, adequate preventive, control measures, and adequate funding. Over the past decade, nine countries have experienced an increase in malaria cases but this is more noticeable in Venezuela. She identified some of the challenges limiting progress of the malaria elimination agenda in Venezuela as political instability and socioeconomic collapse which has increased cross-border malaria transmission in neighboring countries; high biodiversity and distinct feeding behavior of the mosquitoes enhances transmission of the disease; deforestation and illegal mining increases mosquito breeding sites; limited diagnostic methods; antimalarial drug policy and outbreak of COVID-19 epidemic. She concluded by reiterating key gaps that need immediate attention and recommendations for elimination of malaria in the Americas.

Rajesh Panjabi (President's Malaria Initiative - PMI, United States of America) congratulated those involved in the RTS,S/AS01 malaria vaccine production; a significant milestone towards malaria elimination. Panjabi advocated for the continued use of the vaccine with other malaria control tools. He then enumerated the challenges facing malaria eradication: insufficient coverage, increasing costs and insufficient funding, setbacks caused by the COVID-19 pandemic, constant changes in vector and parasites, civil conflicts that hamper elimination strategies and climate crises. However, success in reducing mortality rates has been achieved in 22 PMI countries within Africa. PMI has partnered with sub-Saharan African countries in order to address malaria-based challenges. They have adopted a subnational approach to elimination that is being used to ultimately reach national elimination. Panjabi outlined PMI's focus areas as reaching the unreached; strengthening community health systems; keeping malaria services resilient against current and emerging threats; innovating and leading by leveraging new tools and shaping global priorities to end malaria faster, and investing locally. In conclusion, he acknowledged the efforts of the Africa CDC and challenged us to relentlessly pursue malaria elimination so as not to succumb to the ideology and satisfaction of malaria control.

Corine Karema (National Malaria Control Program - NMCP, Rwanda) began her talk by firstly, reminding us why malaria eradication matters and secondly, telling us about the efforts Rwanda has made to reduce its malaria incidence rates. Rwanda's malaria reduction is attributed to the combined effective use of innovative and transformative tools as well as applying lessons learnt from the COVID-19 pandemic. Karema mentioned that deploying the right prevention tools at the right time to the right places is fundamental to malaria elimination, especially in high-burden countries. This is possible by improving program management, designing strong and sustainable systems and empowering local capacity for efficacious implementation and service delivery. The COVID-19 pandemic emphasised these approaches as countries that valued and invested in strong governance, strategic monitoring, health systems and frontline workers were better positioned to mitigate risks and losses. This is a challenge in Africa where most healthcare systems are fragmented, consequently, disease preparedness and monitoring is fragile thus recovery from severe disease outbreaks is gradual. Currently, many opportunities paving the way for malaria eradication exist and Karema believes that these tools will make it possible to end malaria in a generation.



Pedro Alonso (WHO Global Malaria Programme, Switzerland) began his presentation by applauding the efforts made by China towards malaria eradication. It was from this that Alonso wanted to draw out elements that can aid in achieving malaria eradication. He then defined malaria elimination and stated how the number of countries that are achieving certification continues growing. Certification requires that a country fulfils the strict eradication criteria and evaluation process which includes having no indigenous malaria cases for three years. China, once a malaria endemic country, was able to achieve this phenomenon. It focused on a comprehensive disease prevention and control system, stratified effective implementation strategies and invested in its socio-economic development. From their efforts, Alonso highlighted six principles of elimination that China used and five lessons learnt from countries that have already eradicated malaria. The key element mentioned was adopting a 'Whatever it takes!' attitude. Alonso concluded his motivating presentation with a quote from Boyd (1939), "*Malaria control should not be a campaign, it should be a policy, a long term program. It cannot be accomplished by spasmodic effort. It requires the adoption of a practicable program, the reasonable continuity of which will be sustained for a long term of years.*"

Symposium #60: Malaria: Data to Inform and Target Malaria Elimination Strategies

Rodrigo M. Corder (University of Sao Paulo, Brazil) presented work on the contribution of low-density and asymptomatic infections to *Plasmodium vivax* transmission in the Amazon. The main question Corder tried to answer was: "What is the relative contribution of sub patent and asymptomatic infections to *P. vivax* transmission in the Amazon?" Results showed that 60.7% of PCR-diagnosed infections were missed by microscopy and 70.9% were asymptomatic in 34 population-based surveys across the region. The top 20% spreaders in the 4 sites, two in Peru and two in Brazil, were estimated to contribute between 78.8% and 92.9% of all *P. vivax* transmission events in each site. By estimating the relative contribution of low-density and asymptomatic infections to *P. vivax* transmission in the Amazon, they inferred that subpatent parasite carriers contribute little to the overall transmission in their study population. Potential implications for malaria elimination strategies in this region are understanding that conventional microscopies may suffice to identify the vast majority of infections that contribute to human-to-mosquito transmission of *P. vivax* and that ultra-sensitive molecular techniques may not be a fundamental component of malaria elimination programs in the region.

Prayuth Sudathin (University of Public Health, Thailand), began his presentation on using source of infection data to target malaria elimination in Thailand by highlighting the background of malaria elimination strategy surveillance and response approach which prioritise evidence-based employment in the country. The study adopted the routine data of 2016-20, which was used to assess whether associations increase infections and understand validity in identifying remaining hotspots. Data of interest for associations included population and demographic characteristics, human movement and travel history compiled using the Chi-square test. During the study period, transmission due to outside and imported cases showed a decline. However, reconciliation showed more demographic cases for preschool, school children and elderly women also known as dependent groups. Outside transmission was associated with young adults and adult groups, male, and non-Thai-migrants. In the study, the population was divided into outside, imported transmission and also indoor transmission species groups. The number of imported cases remained consistent all the time. Therefore, sole infection data along with travel date and clinical history can be used to know the origin of cases and detect epidemiological linkage of cases, which would enhance efficacy and use of limited cases. Sole infection data could be used to tailor specific interventions.

Maylis Douine (Cayenne Hospital, French Guiana) presented the results of an operational research study in the Amazon on self-diagnosis and self-treatment for malaria known as the Malakit Project. French Guiana is in the Amazon Guiana shield of South America where the soil is rich in gold, hence attracting a lot of miners with high malaria prevalence. The main objective of the study was to understand and increase, the use of early and adaptive treatment with good compliance, with a secondary objective to improve knowledge of practices and decrease malaria prevalence. The distribution and training of Malakit use were done by facilitators from the target population for 2 years. The study employed cross-sectional and qualitative survey data collection for participants' opinions on the use of the kit. Results indicated that more than 70% of people correctly used the kit. Testing before treatment certification increased and the proportion of *Plasmodium falciparum* decreased before and after intervention compared with PCR prevalence of *Pf Impact* evaluation on malaria epidemiology. Douine concluded that the impact on malaria incidence estimates that Malakit prevented 46% of imported cases.

May Me Thet (Population services international, Myanmar) presentation was about the role of rural private sector providers in malaria surveillance and case management during the COVID-19 pandemic in Myanmar. Myanmar has 3 types of health providers named: health quality medical doctors channeled practitioners based in urban areas, trained informal providers called private armlets, and community volunteers, working in rural areas. During the COVID19 pandemic, service provisions were affected in both the private and public sectors. The study evaluated the performance and quality of the 3 service providers of service before and after the pandemic. Data analyzed were generated using a routine management information system database that incorporates clinic data, private outlets and volunteers. Audit testing and positive case findings, as well as service quality scores, were used to compare service providers. Results highlighted that performance in medical doctors' audit testing per month decreased while private outlets testing increased, and that service scores were similar among the 3 service providers which were statistically significant.

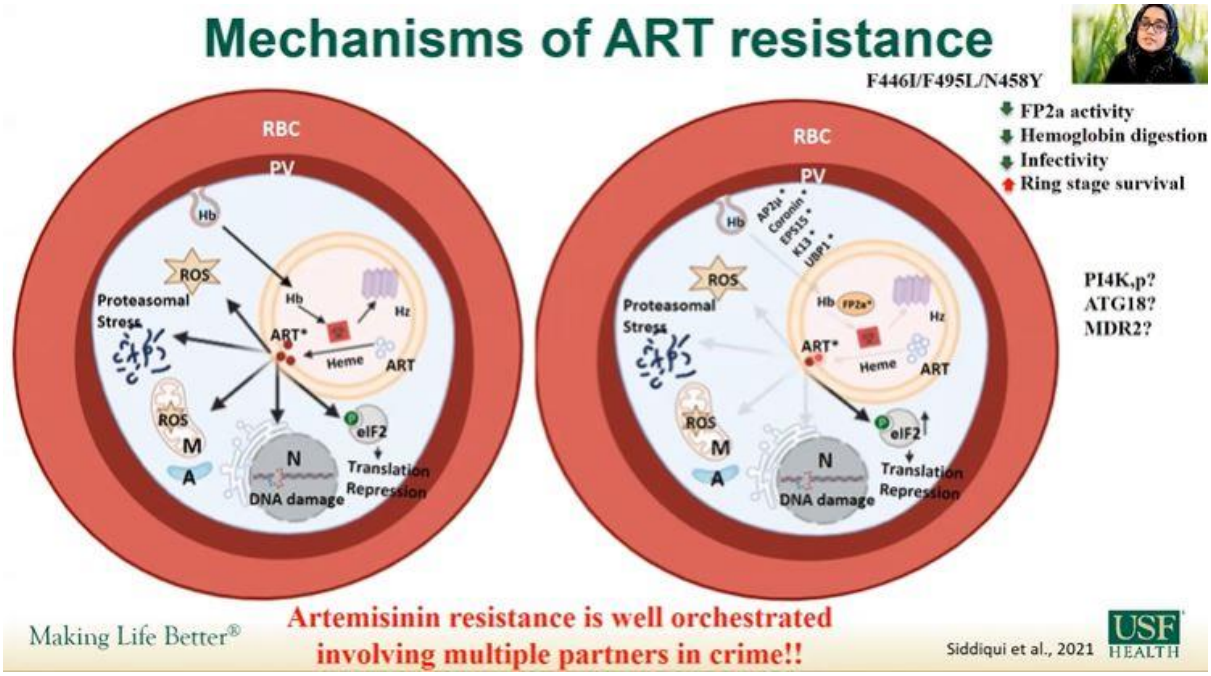
Will Stone (London School of Hygiene and Tropical Medicine, England) presented on gametocyte persistence, infectivity and associations with histidine-rich protein 2 (HRP-2) levels after pyronaridine-artesunate and dihydroartemisinin-piperaquine with and without single-low dose primaquine, assessed using a single-blind randomized clinical trial in Ouelessebougou, Mali. The primary endpoint was within arm reduction in the proportion of mosquitoes infected by participant blood samples 48 hours' post-treatment. Secondary endpoints included infectivity to mosquitoes at other time points, measures of gametocyte density and sex ratio and safety measures including the frequency of adverse events and hemoblogin concentration. Infectivity to mosquitoes was measured using direct

membrane feeding assays which found infectivity stopped almost immediately in arms with PQ; 10-20% of individuals were still infectious after 21 days with ACT alone. They also tested HRP2 detectability because gametocytes continue to circulate in the blood for long periods after standard ACT treatment. Stone concluded that results found no significant differences in HRP2 concentration determined by Quansys ELISA between ACT treatment groups with or without primaquine and there were no differences.

Erica Berlin (Clinton Health Access Initiative - CHAI, United States of America) presented on the use of qPCR and serology to inform targeting malaria elimination strategies in low burden settings in Botswana. A Malaria Transmission Limits Survey (MTLS) was implemented in 3 districts in 2018 with the objectives of determining whether malaria transmission was present and at what intensity, to determine the limits of malaria transmission by detecting current and past infections, and to describe potential factors associated with malaria transmission by administering a questionnaire. Populated blocks of 5x5 km were identified that contained at least 10 structures; they were prioritised according to high risk or high uncertainty as to risk based on incidence estimates. Based on the survey, estimated qPCR-prevalence of malaria in the peak season was <0.1% for all 3 districts. Overall, 20% of adults surveyed were seropositive; lower seropositivity in participants under 18 years suggest that transmission has decreased markedly over the past 2 decades. The majority of people with high antibody response had not travelled in the past month, but the small number that did, travelled within Botswana, indicating local transmission. In conclusion, Berlin said that transmission appears to be declining over time, there is low risk of importation and reintroduction, and serology and qPCR confirmed findings from the case-based surveillance system that fishermen and farmers are the most exposed.

Symposium #65: Malaria: Drug Treatment, Resistance and Clinical Trials

Faiza Siddiqui (University of South Florida, United States of America) discussed various ways to deeply explore molecular markers involved in artemisinin resistance with a great focus on PfK13. Siddiqui and team used a green fluorescent protein to study the expression and localization of PfK13 protein in asexual and sexual stages. Some of the K13 mutations tested show lower fitness and higher ring stage survival under drug pressure They used a new antibody against PfK13 to show that the PfK13 protein is expressed ubiquitously in both asexual erythrocytic stages and gametocytes and is localized in punctate structures, partially overlapping an endoplasmic reticulum marker. She partially concluded that some parasites showing resistance phenotypes lack K13 mutations. Siddiqui highlighted the need to identify additional markers of resistance. Artemisinin resistance selection using Dd2 strain and genome sequencing has identified SNPs in other genes (e.g. PI4K, ATG18 or MDR2). Further studies determining all contributors towards resistance are needed.



Melissa Rosenthal (University of Nebraska Medical Center, United States of America) started her presentation by establishing a relation between *Plasmodium falciparum* and various peroxides including artemisinin, arthemether and artesunate. She talked about various protein damage caused by artemisinin in parasites resulting in accumulation of ubiquitinated proteins which are then degraded by the parasite proteasome. She presented both non-selective proteasome inhibitors and *Plasmodium*-specific proteasome inhibitors. Then, Rosenthal hypothesized that the proteasome is critical for parasite ART-response and mutations decreasing proteasome catalytic activity reduce the ability of parasites to recover following ART-induced protein damage. Proteasome mutants exhibit decreased β2 and β5 catalytic activity in response to dihydroartemisinin (DHA). Rosenthal's team found that β5 A20S does not compromise peroxide potency and increases synergy in some peroxide combinations. On the other hand, β2 proteasome mutants display increased sensitivity to DHA and the related endoperoxide OZ439. She also reported an increase in sensitivity observed not only at early ring stages where ART resistance is classically observed but also at trophozoite stages and in asynchronous cultures. The sensitivity throughout the intraerythrocytic development is likely due to the necessity of the parasite proteasome throughout its lifecycle. She highlighted the importance of the parasite proteasome in response to endoperoxides.

Recently, resistance to the antimalarial artemisinin has been reported in Uganda, posing the threat of the emergence and spread of artemisinin resistance in Africa. **Jean Moïse Tanga Kabore** (Health Action Research Group - GRAS, Burkina Faso) presented a pilot study that aims at assessing the feasibility of a strategy deploying simultaneously three artemisinin-based combination therapies (ACTs) at health facility (HF) level for the management of uncomplicated malaria in Burkina Faso. Strategy was aimed at delaying the spread of resistance to ACT treatment. The study population was segmented in 3 groups receiving at HF-level either pyronaridine-artesunate (patients under 5 years), dihydroartemisin-piperaquine (5 years and above), or artemether-lumefantrine (AL) (pregnant women). The community case management of malaria continued with no change using AL. Tanga showed that over the 12 months of the study, 182,247 and 4,955 malaria cases were seen at HF and community level respectively and treated with ACTs. No serious adverse drug reaction was reported. The compliance with the multiple first-line therapies (MFT) protocol guidelines was adequate for three quarters of health workers (HWs) and there was a good management of ACT stocks over the study

period. He concluded that the implementation of an MFT strategy in Burkina Faso is feasible and well accepted by the HWs, and that a scale-up is conceivable.

Mackenzie Sievert (Eck Institute for Global Health, United States of America) mainly discusses the improvement of the ring stage survival assay (RSA) serving artemisinin resistance measurement. He presented different assay modifications that increase efficiency and/or precision of this assay. Sievert and team adjusted culture volumes, synchronization and used improved equipment (flow cytometer, 96 well plate and qPCR) then developed a modified RSA. This tool improved correlation with patient clearance half-life and significantly reduced experimental noise and labor intensiveness. This also allowed the higher throughput needed to quickly phenotype large numbers of parasites in less time. He conducted several experiments; resistance was inferred at 120hours as a differential between treated and untreated parasites then combined with an additional 192h post-treatment sample to generate a recovery profile. He reported that recovery expands their view of the drug response phenotype. This study reveals that the growth, resistance and recovery assay combines more detailed fitness phenotypes, greater correlation to clinical phenotype and additional drug response phenotype to differentiate sensitive parasites. This serves as a novel and complementary phenotype to resistance that quantifies a parasite's ability to tolerate drug exposure, a hallmark of parasite response to ART.

M5717 is an antimalarial compound acting on all life stages of the malaria parasite, and inhibiting the *Plasmodium falciparum* elongation factor 2 (PfeEF2). **Johan van der Plas** (Centre for Human Drug Research, the Netherlands), presented the results of a Phase Ib, randomized, double blind, sequential, adaptive dose-finding study to assess M5717 chemoprophylactic activity in healthy male and female volunteers inoculated with *P. falciparum* sporozoites. The initial cohorts followed a dose de-escalation pattern and the effect of single doses ranging from 200 to 30 mg was evaluated. The study showed that M5717 is well tolerated, and that there were no potential risks or safety concerns whatever the dose compared to existing clinical data. The safety profile did not indicate any treatment of emergent adverse events (TEAE) leading to death or discontinuation, and no serious IMP-related TEAEs. Van der Plas then presented the proof of chemoprophylactic activity of M5717, showing that a single dose of ≥ 100 mg provided 100% protection in liver-stage controlled human malaria infections. There was no evident difference in protection rate in early and late liver-stage models. Altogether, the results of the study warrant further development of M5717 as part of a chemoprevention combination for malaria and can guide rational dose selection in prophylactic clinical trials.

Tafenoquine (TQ) is a long-acting 8-aminoquinoline that has activity against hepatic stage schizonts, and *Plasmodium vivax* hypnozoites, as well as less well-characterised activity against blood stage parasites and gametocytes. **Bridget Barber** (QIMR Berghofer Medical Research Institute, Australia) presented a 2-part study investigating the effective dose of TQ to clear blood-stage *P. falciparum* parasitaemia (Part 1), and to prevent transmission *of P. falciparum* to mosquitoes (Part 2). Part 1 results showed that low dose (300 mg) of TQ was not efficacious at clearing asexual parasitaemia in healthy volunteers experimentally infected with blood-stage *P. falciparum*. The development of a PK/PD model is underway and preliminary results show that none of the participants treated with TQ 200 mg achieved complete parasite clearance, while the model shows efficacious dose prediction for participants treated with 300 mg TQ higher dose will be needed (6 log kill: 520 mg; 9 log kill: 850 mg). In the second part of the study, she showed that 50 mg TQ reduced transmission intensity by 75% by day 7, and that there was a good correlation between oocyst and sporozoite positivity rate. Further studies are underway to address limitations and remaining questions, such as how results translate to field settings, or the duration of the transmission blocking effect.

Artemisinin-combination based therapies (ACTs) are threatened by the emergence and spread of *Plasmodium falciparum* parasites less susceptible to artemisinin derivatives and their partner drugs. **Thierry Masserey**'s (Swiss Tropical and Public Health Institute - Swiss TPH, Switzerland)

research work consists of identifying the key drivers of establishment and spread of malaria parasites. He presented the results obtained using an adapted stochastic individual-based model of malaria epidemiology and transmission dynamics that allows the systematic quantification of the influence of biological, transmission settings, health systems, and pharmacokinetics/ pharmacodynamics factors on the establishment and spread of drug-resistant parasites. The spread of resistance to artemisinin extends because parasite exposure to artemisinin derivatives when used in monotherapy and delays the evolution of resistance to the partner drugs when used in combination therapies. When used in monotherapy, the spread of resistance to partner drugs reduces the selection pressure caused by the period of low drug concentration. Low transmission intensity favours the evolution of drug-resistance. Masserey concluded that the resistance to the partner drug has an essential role in promoting evolution of resistance to artemisinin. These results could have implications for delaying resistance to artemisinin by ensuring adherence to treatments and that no resistance to the partner drug exists in the target population, and for informing future artemisinin therapies using additional long-acting drugs as partners to minimize the selection window.

Symposium #71: Challenges in Malaria Diagnosis

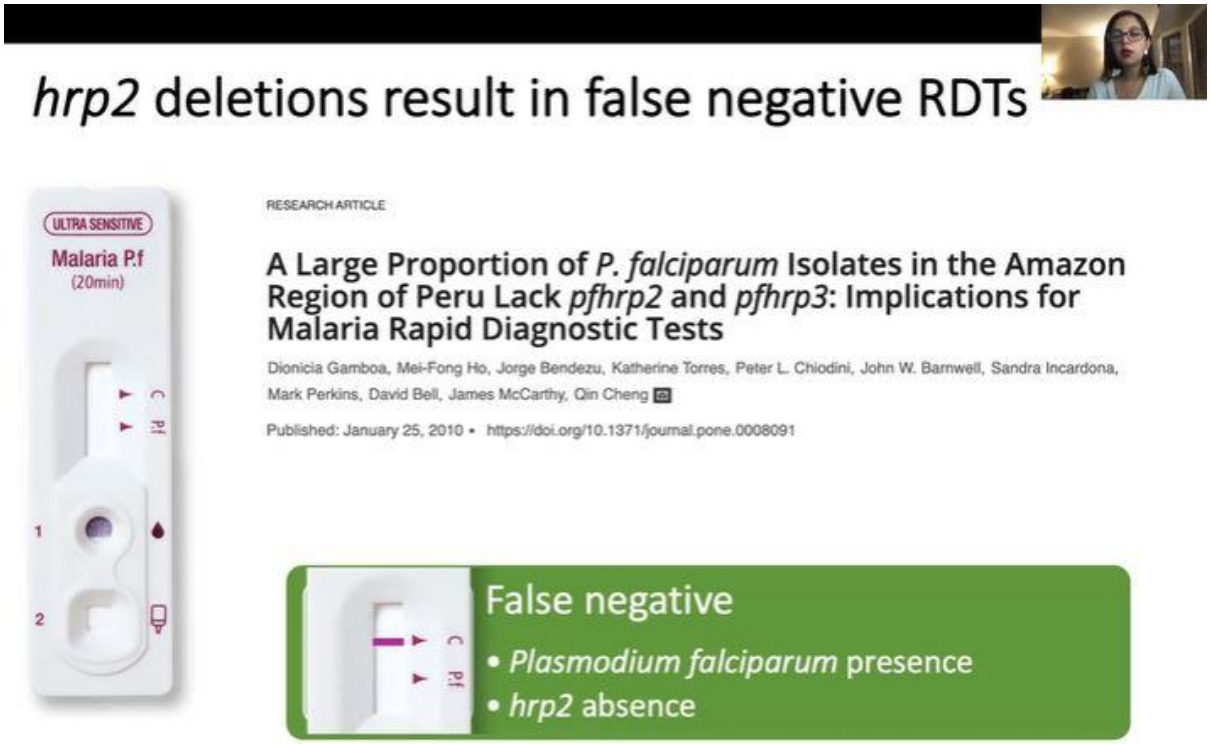
Jessica McCaffery (Centers for Disease Control and Prevention, United States of America) presented a study titled, 'Use of a Novel *Plasmodium vivax* Chimeric Protein for Malaria Serosurveillance in Multispecies Endemic Countries Nearing Elimination'. McCaffery presented results from a proof of concept study that was conducted in USA travelers returning from malaria-endemic countries with PCR confirmed parasitemia. They used chimeric PvMSP1 (cPvMSP1) to capture IgG and found that cPvMP1 was recognized by the majority of these PCR positive travelers regardless of species causing infection. After confirming that cPvMSP1 can capture malaria-specific IgG in infected travelers more broadly and with higher signal than recombinant PvMSP1 (rPvMSP1), they conducted a seroprevalence study in two malaria endemic areas nearing elimination in Ethiopia and Costa Rica. Results showed that seroconversion rates reflected malaria transmission history of the study sites. Ethiopia's seroconversion model suggested cPvMSP1 may detect both *P. falciparum (Pf)* and *P. vivax (Pv)* infections combined or showed increased sensitivity of cPvMSP1 over rPvMSP1, while in Costa Rica's seroconversion was detected earlier for cPvMSP1 than rPvMSP1. McCaffery described the benefits of engineered antigens by highlighting its ability to be tailored to determine pan-*Plasmodium* exposure or for species-specific detection as it can be designed to include highly recognized epitopes resulting in increased sensitivity and accuracy of detection. She concluded that multiplex assays offer a way to estimate malaria transmission, and using engineered antigens alongside established recombinant antigens in multiplex seroprevalence studies can help to identify high-transmission areas.

Dean Sayre (Centers for Disease Control and Prevention, United States of America) pointed out that Cambodia had the second-highest number of malaria cases in GMS in 2020. Although intense national efforts have helped in reducing malaria cases in the past few years, *Pv* cases are still accounting for most of the cases in Cambodia. The country is aiming to eliminate *Pf* by 2023 and *Pv* by 2025. Considering the unique ability of *Pv* to become dormant in the liver stage, elimination efforts require intervention specifically for tackling the hypnozoites. Although primaquine and tafenoquine can eliminate hypnozoites, these drugs can cause destruction of red blood cells, or hemolytic anemia, in individuals with inadequate amounts of the enzyme glucose-6-phosphate dehydrogenase (G6PD) deficiency, which can be lethal in some cases. Sayre presented results from clustered, cross-sectional surveys of adults from the Kampong Speu province, that evaluated the performance of the quantitative point-of-care (POC) G6PD activity assay STANDARD™ G6PD (SD Biosensor, Republic of Korea). The study consisted of two phases, a community phase and a health-facility phase. The POC, which uses capillary blood, was compared against the gold standard laboratory method (spectrophotometry) that used venous blood. In the community phase, the POC assay was 93% (85–

100%) sensitive for detecting individuals with ≤ 30% median G6PD activity (negative predictive value, NPV = 99% (98—100%)). Using ≤ 70% median G6PD activity as the cut-off, POC sensitivity was 65% (53-78%), with NPV = 88% (81—94%)). Results from the community phase resulted in modifications in specimen transportation procedures for the health-facility phase. Data for this phase is preliminary but suggests that the POC assay can accurately identify those at the highest risk of primaquine-induced hemolytic anemia.

Han Zhang (Harvard University, United States of America) presented a study on the impact of malaria rapid diagnostic tests scale-up on antibiotic use in 21 sub-Saharan African countries. Here, they constructed a dataset with related individual-level information from 3 data sources (demographic and health surveys, the Malaria Indicator surveys, and the Multiple Indicator cluster surveys) and explored the variation in mRDT distribution from a major donor - U.S President's Malaria Initiative (PMI) over a 10-year period (2009-2019). Results showed that PMI total mRDT distribution across study countries was about 496.7 million, with huge variation across countries and a dramatic scale-up over the period. This study further determined a correlation between PMI mRDT distribution scale-up and increased testing uptake for children <5 years with fever. She highlighted that mRDT scale-up had a heterogeneous impact on antibiotic use by malaria parasite prevalence and by place of care. Zhang concluded that work is ongoing to explore the health implications resulting from the change in antibiotic use as well as improvement measures on regional-level mRDT distribution.

Rapid diagnostic tests (RDT) are easy-to-read devices with field applications in malaria. Common RDTs target the Histidine-Rich Protein 2 (*hrp2*) antigen, but many countries report parasites with *hpr2/hrp3* gene deletions, undetectable by these RDTs. **Claudia Vera-Arias** (University of Notre Dame, United States of America) used digital droplet PCR (ddPCR) for the molecular surveillance of *hrp2/hrp3* deletions to circumvent the difficulties of nested PCR (nPCR). A novel dPCR was optimized on 2 systems (BioRad QX200 and Qiagen Qiacuity). The assay was compared to nPCR using triplicates of 248 samples of asymptomatic infections from western Kenya, nPCR gave 12.3% false-negative results when compared to ddPCR. Also, mixtures of lab strains with the *hrp2* deletions (Dd2) and wild-type (3D7) were used to test the effect of polyclonal infections. ddPCR reliably detected mixed infections if mutated parasites were >40%. The new ddPCR assay was used to type samples from Kenya (241), Zanzibar (Tanzania) (91), Ghana (223), Ecuador (41), Brazil (187), and southwestern Ethiopia (47). No deletions were observed in Kenya, Ghana, and Tanzania; in Ecuador, no *hrp2* deletions were observed, but 53.7% of samples carried *hrp3* deletions. In Ethiopia 2.1% carried a *hrp2* deletion, and 74.5% hrp3 deletions (2.1% *hrp2/hrp3* double deletion) and, in Brazil, 46.5% of samples carried *hrp2* deletions, and 62% *hrp3* deletions (46% *hrp2/hrp3* double deletions).



Near-infrared spectroscopy (NIRS) has been previously applied in mosquito surveillance to identify and characterize types of malaria infections. **Maggy Sikulu-Lord** (The University of Queensland, Australia) presented the results on the evaluation of a rapid, reagent-free, and non-invasive malaria detection tool based on NIRS. Using a mouse malaria model, infrared light was shined briefly on the ears, feet, groin, and tail of mice with and without *Plasmodium berghei* malaria infection at multiple time points to collect reflected spectral signatures. Mice were divided in two groups and were scanned before (0 hrs) and after (24, 48, and 72 hrs) infection. Machine learning was then applied to differentiate infected from uninfected mice. Positive predictive rate (PPR) and negative predictive rate (NPR) of NIRS were 90% and 100% when parasitemia levels were ≥2%, being consistent with microscopy results. Using the same principle, a handheld NIR spectrometer was used to scan arms, fingers, and ears of 12 human volunteers who were either uninfected or infected with *P. falciparum* or *P. vivax*. The model built by machine learning detected infections with 100% sensitivity and 83% specificity. Sikulu-Lord emphasized that, although the results are promising, more data from the field will be required to verify the diagnostic capacity of NIRS.

Wataru Kagaya (Osaka City University, Japan) discussed a study conducted in 2020 at the Homa Bay County referral hospital in western Kenya. The goals of the study were to 1) apply XN-31p for mass malaria surveillance in the field; 2) test its applicability to capillary blood samples; and 3) evaluate the effect of sample storage time and temperature on results stability. Capillary and venous blood samples collected from 169 outpatients in which clinical malaria was suspected were tested with XN-31p, microscopy, RDT, and PCR. The sensitivity and specificity of XN-31p with capillary blood samples (using PCR as the gold standard) were 85.7% and 100%, respectively, with results being comparable to RDT and microscopy. Results with the XN-31p maintained stability in samples assayed 24 hours' post-collection, and capillary and venous blood samples showed concordance. Kagaya added that an advantage of XN-31p is that it is automated, so there is no need for special training to use it. As the next step, his team intends to assess the performance of XN-31p against asymptomatic or submicroscopic infections and for the diagnosis of *Pf* and non-*Pf* mixed infections.

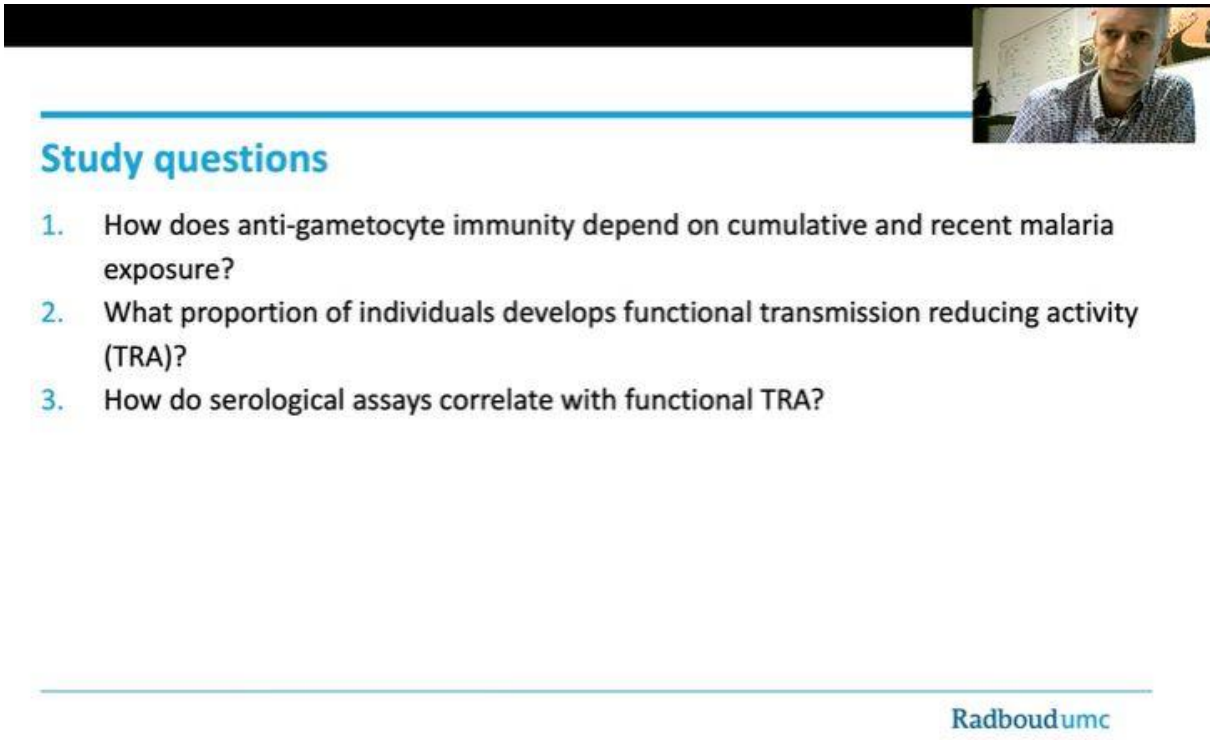
Retno Utami (Eijkman Institute of Molecular Biology, Indonesia) presented a study entitled 'Identifying future *Plasmodium vivax* relapses with serological markers of exposure in a returning Indonesian soldier cohort'. She explained that *Pv* is endemic in the Indonesian archipelago, where the proportion of *Pf* to *Pv* cases is approximately 1:1. Blood samples were collected from a cohort of 294 Indonesian soldiers at high risk of acquiring malaria infections who were free of acute *Pv* infection by microscopy after returning to the non-malarious area of East Java after a tour-of-duty in the moderately malaria-endemic area region of Papua. Enrolled participants were followed by active and passive surveillance for the first 6 months after returning to East Java. Serology for 19 exposure markers was conducted in all enrollment and follow-up samples by Luminex. Using random forest classification, a panel of eight serological exposure markers (SEMs) showed 75% sensitivity and 93% specificity in identifying individuals with hypnozoite and those at risk of future relapse infections during the 6-month observational period. Thus, SEMs successfully identified malaria-exposed but uninfected individuals at risk for subsequent relapse infections.

This report is brought to you by the MESA Correspondents Edima Ottoho, Tope Kayode, Franklin Tembongshu Formilack, Lucy W. Mwangi, Vita Mithi, Ana Alonso, Faith Hungwe, Olajoju Temidayo Soniran, Isabelle Delrieu, Doumbe Belisse Patricia and Carlos A. Fernández Miñope, with mentoring and editorial support from Divya Beri.

Day 4: 20th November 2021

S #85: Malarial Immune Response from Numerous Perspectives

Malaria transmission depends on *Plasmodium* gametocytes and naturally acquired antibody responses to gametocyte antigens (i.e., Pfs48/45 and Pfs230) which can reduce this transmission. In a study presented by **Teun Bousema** (Radboud University Medical Centre, the Netherlands) anti-gametocyte immunity was assessed by serological analysis and functional standard membrane feeding assay (SMFA) using plasma samples collected regularly from 433 cohort participants residing in Tororo, Uganda. Malaria transmission declined over the 6-year study period due to highly effective prevention. Bousema presented preliminary results indicating a high prevalence of antibodies against Pfs230 (39.5% in children under 5, 65.3% in 5-11 years, and 84.9% >18 years). For Pfs48/45, antibody prevalence was 13.4%, 44.6%, and 76.0%, respectively. Compared to parasite-free individuals, anti-Pfs48/45 antibody prevalence was higher in those with sub-microscopic infections, microscopically-detected infections, or microscopically-detected gametocytes. Eleven samples out of 263 fully blocked transmission in the SMFA. The surface immunofluorescence assay (SIFA) is particularly discriminative and predictive. Bousema concluded that these results show that anti-gametocyte antibody responses are acquired with increasing cumulative exposure and associated with recent exposure. Intriguingly, age-dependent antibody patterns were not mirrored by an increase in functional transmission reducing immunity. Additionally, SIFA may be a useful tool for SMFA pre-screening and use in epidemiological studies. Ongoing work will better examine the kinetics of functional immunity to gametocytes and may inform the development and deployment of transmission-blocking vaccines.



Jason Nideffer (Stanford University, United States of America) began by showing how males, aged between 5 and 15 years, had a better and longer immune tolerance towards *Plasmodium* infections in contrast to females of the same age. In the study, 26 female and 23 male participants from Uganda were recruited. His study used flow cytometry, high throughput Luminex-based magnetic bead-based assay, and single-cell transcriptomic RNAseq to assess immunological responses. The data showed that males produced more pro-inflammatory cytokines in response to Toll-like receptor (TLR) stimulation. Interestingly, all participants that were previously exposed to malaria expressed a

heterogeneous population of CD123+ myeloid cells, however, this was more in males than in females. The CD123+ cells, commonly associated with plasmacytoid dendritic cell expression, expressed CD11c; a myeloid marker, which significantly altered the myeloid compartment. It was noted that cytokine and HLA-DR cells were expressed consistently by the CD123+ population. The effect of CD123+ myeloid compartments on host immunity revealed inconclusive results, however, females aged 7 - 11 were found to have higher titres of IgG against merozoite surface proteins 1 and 2 suggesting females might have advanced immune responses against malaria and other parasites. Nideffer concluded his talk by expressing his intentions of looking into how CD123+ cells may prime the male adaptive immune response.

Clinton Onyango (University of New Mexico-Kenya, Kenya) spoke about how severe malarial anemia (SMA) has resulted in a high mortality rate in children aged 3-36 months. Low haemoglobin (Hb) has caused inefficient erythropoiesis and numerous innate pathways have been associated with SMA pathogenesis. This study aimed to characterise SMA pathogenesis pathways by sequencing the entire expressed transcriptome of both non-SMA (Hb>7.0 g/dL) and SMA children (HB<6.0 g/dL). An enrichment analysis was conducted to identify the top emerging pathways and the IL-5 signalling via the JAK/STAT pathway was determined as the top-ranked differentially regulated pathway in children's SMA pathogenesis. IL-5 is involved in several innate and adaptive responses. The results obtained showed that impairments within the IL-5 negative feedback loop can inhibit the JAK/STAT pathway whilst diminished B cell differentiation and maturation and class switch recombination cause an inability to generate appropriate adaptive immune responses. Lastly, Onyango's results showed that transcriptional analysis suggests that SMA may disrupt processes that inhibit apoptosis.

Isobel Walker (University of Melbourne, Australia) talked about how malaria antibodies are acquired with exposure to infection and age and attack varying parasitic antigens such as *Plasmodium falciparum* erythrocyte membrane 1 (PfEMP1). These antibodies modulate parasitic binding and sequestration in blood cells and vessels. PfEMP1 has several phenotypes with domains that are associated with severe or uncomplicated malaria (UM). The aim of this study was to determine whether a subset of 33 PfEMP1 domains are associated with cerebral malaria (CM). The study screened antibodies of 98 Malawian children admitted with either CM or UM using a multiplex immunoassay method. The screening aimed to determine the quantity and quality of the fragment crystallizable region (FcR) of antibodies. The FcR may be indicative of the protective functions of the antibody. Walker's study found that antibodies were able to accurately (83%) predict the clinical outcome of PfEMP1 antigens. She also noted that antibodies that bound to ICAM1 and CD36 binding, as well as rosetting PfEMP1, were associated with UM whilst those that bound to DBLδ1 PfEMP1 types were correlated with CM. IgG2 and IgG4 titres as well as specific antibodies that engaged with FcRs found on monocytes and neutrophils were also associated with UM.

Although *Plasmodium vivax* is the most common malarial species worldwide, it remains rare in Sub-Saharan Africa. Since *P. vivax* must bind to the Duffy antigen receptor expressed on host erythrocytes for merozoite invasion, the absence of *P. vivax* infection may be due to elevated levels of Duffy negative individuals on the continent. **Lauren Bradley** (Case Western Reserve University, United States of America), presented the results of a study that explores *P. vivax* naturally acquired immunity in Duffy negative individuals. More specifically, she studied malaria burden, seroreactivity and seroprevalence across Duffy phenotypes, and analysed clustering effects of antibody response on Duffy expression. A cross-sectional survey in low transmission endemic areas in Ethiopia allowed collecting samples that were analysed in serologic assays and sequencing for prevalence of malaria, Duffy phenotype and seroreactivity. Lauren showed that Duffy negativity offers strong but incomplete protection against *P. vivax* infection. Individual *P. vivax* antibody development is reduced in Duffy negative people. Duffy negativity correlates with seroprevalence of *P. vivax* antibodies. Taken

together, the data suggest that antibodies against *P. vivax* are less likely to develop in Duffy negative individuals, reflecting lower infection rates in these populations.

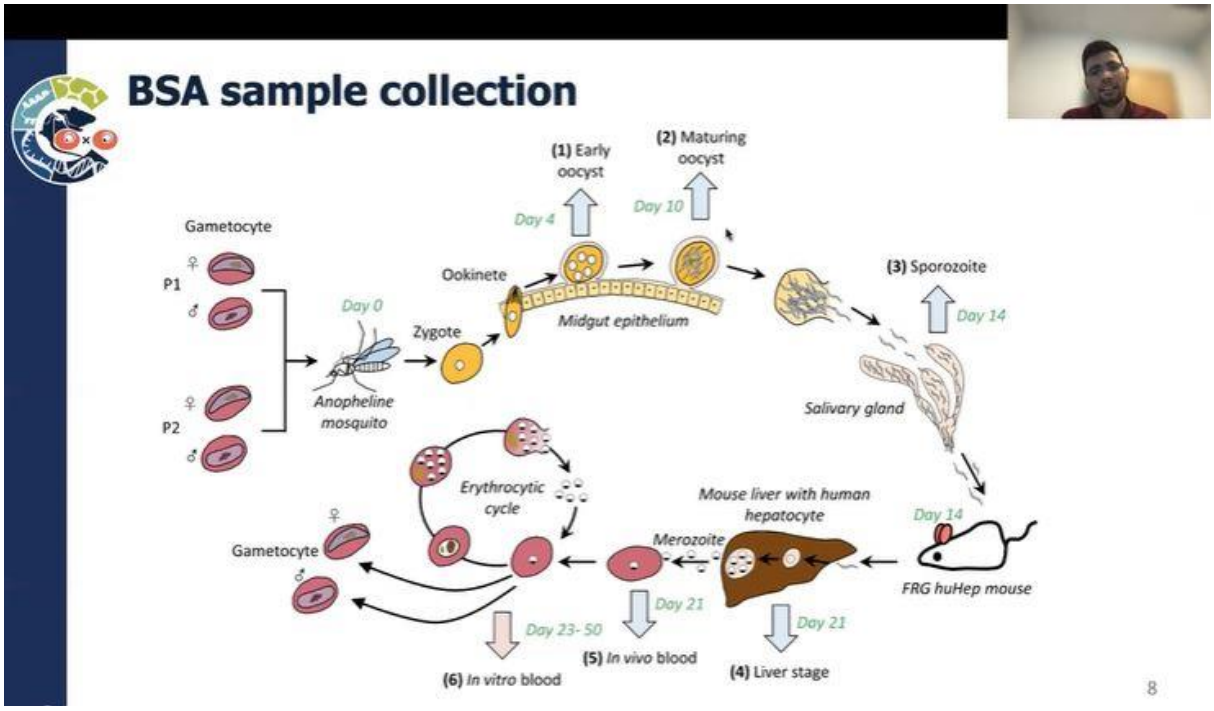
Wael Abdrabou's (New York University Abu Dhabi, United Arabs Emirates) study aimed at evaluating intra- and inter-ethnic and metabolite expression before and during a *Plasmodium falciparum* infection. In his study, a mixed methods approach was used to identify metabolites and to conduct assays. Children from two ethnic groups (Mossi and Fulani and Gouin) in Burkina Faso, aged between 5 and 10 years, were recruited with the Mossi and Fulani tribes being more resistant to malaria. After metabolic profiling was conducted, 92 metabolites associated with parasitemia were used to identify the most perturbed metabolic pathways during infection. From these, 12 steroids were identified and revealed to have a positive correlation with parasitemia whilst a negative correlation with lymphocyte levels was noted. These steroids were found to be immunosuppressive as they inhibited T helper cells signalling pathways and activated T exhaustion signalling pathways. To conclude his talk, Abdrabou summarised that *P. falciparum* induced steroid expression had an immunosuppressive effect on the adaptive immune response T cell functions. However, this would not affect Mossi and Fulani tribes' children due to the heterogeneity in their steroid expression when infected with *Plasmodium.* This variability caused a heightened immune response and reduced susceptibility to *P. falciparum* infection in these tribes.

Fergal Duffy (Seatle Children's, United States of America) gave a brief overview of how the radiation attenuated sporozoite (RAS) vaccination approach works against controlled human malaria infection. As the immunological correlation of RAS-induced protection was unknown, the study aimed to determine the systemic responses correlated with RAS-induced vaccination. To achieve this, the immunisation with radiation attenuated *Plasmodium falciparum* sporozoites (IMRAS) trial was conducted on protected and non-protected cohorts. Samples obtained were subjected to whole blood RNAseq and flow cytometry analysis allowing identification of differentially expressed genes and immune cell phenotyping. High inflammation and interferon modules were observed in the non-protected cohort only after the first immunisation. The high inflammation was correlated with a notably high population of monocyte (ILT3+, CD11c) and dendritic cells whilst high baseline levels of another subtype, ILC2, was associated with type 2 immunity was observed. After the first immunisation, immune cell expression fluctuated. On the contrary, the protected cohort displayed a more consistent expression of immune cells throughout the five immunisations. However, Vδ2 γδ-T proliferated in protected and non-protected cohorts and these cells may have a protective function.

S #88: Malaria: Genetics, Genomics and Modeling

Sachel Mok (Columbia University Medical Center, United States of America) discussed her work on the characterization of a novel resistance mediator to the synthetic ozonide, OZ439 (artefenomel), which is an antimalarial pre-clinical drug candidate currently under analysis. It has been found that OZ439 has a long *in vivo* half-life of 46-62 hours, an advantage over dihydroartemisinin (DHA) which has a half–life of less than 1 hour. She used CRISPR/Cas9 *k13* gene editing to validate the K13 A212T mutation which she identified as a new molecular marker of OZ429 *in vitro* resistance and assessed the impact of the mutation on survival in mutant and wild type parasites. She observed that while K13 A212T did not alter IC_{50} or IC_{90} or ring survival rates to OZ439 or DHA, yet parasites with K13 A212T+R539T mutations recovered faster after 48 hours of OZ439 exposure. Proteomics and metabolomics profiling were performed to elucidate whether the A212T mutation may affect haemoglobin (Hb) catabolism and if this is the primary mechanism of lowered antimalarial activity and OZ439 resistance. She found that A212T neither affects Hb processing, nor impacts peptide regulation in response to OZ439 or DHA. Instead, A212T+R539T mutations enhance cell recovery post drug-removal via the upregulation of metabolites linked to redox, lipid, and aspartate metabolism.

Sudhir Kumar (Seattle Children's Research Institute, United States of America) began by outlining the importance of carrying out *Plasmodium falciparum* genetic crosses, including those that had historically identified PfCRT mutations as a driver of chloroquine resistance. Kumar's group carried out bulk segregant analysis (BSA) to evaluate the change in parental mitochondrial (MT) and apicoplast (Api) genomes by using recombinant progeny pools. They observed a decrease of NF54 MT allele frequency in the cross of NF54xNHP4026 during the transition from sporozoite to liver stages, a phenomenon that had not been seen before. The study concluded that progeny from allopatric crosses differ in MT/Api inheritance while sympatric crosses do not. Further investigation to generate progeny with NF54 MT/Api genomes by crosses of male sterile NF54 and female sterile NHP4026 parasites, as well as to determine if MT inheritance in the recombinant progeny is associated with regions of nuclear genome inheritance will be conducted.



Angela Early (Broad Institute, United States of America) talked about the epidemiological history of *P. falciparum* (*Pf*) in the Pacific Coast Region of South America. She presented the genomic profiling of *Pf* on Colombia and Ecuador Pacific Coast. They analysed 161 whole genome sequences from monoclonal infections sampled in Colombia and Ecuador collected between 2013 and 2016, where 60% and 10% of malaria infections are *Pf*, respectively. Sequencing confirmed high relatedness and low haplotypic diversity. Six of these clusters have persisted for at least 10 years, but the population as a whole is not static, as there is evidence of *de novo* mutations. She analysed chromosomal segments between pairs of samples and identified five putative crosses among 11 of the 17 genomes sampled after 2012. Two of these crosses generated novel combinations of drug-resistance haplotypes. She coupled this with epidemiological data and found that the timing of crosses likely coincided with a period of high transmission. She observed that the recombination patterns support a hypothesis of outbreak-driven outcrossing and generated new combinations of resistance markers. Using identity-by-descent (IBD) analysis, she confirmed the decades-long persistence of *Pf* clones along the pacific coast of Colombia and Ecuador.

Jessica Ribado (Institute for Disease Modeling, United States of America) described epidemiological and genetic models of malaria transmission to understand transmission history and features of transmission. At the onset of her presentation, she stated that models help us take what we know about an environment and turn it into actionable information. In her analysis, she combines EMOD, a

detailed stochastic agent-based model for simulating malaria genetic epidemiology with Genepi to give information about each unique strain in an infection, and feeds into an observational model. Observational models can interrogate variant properties of sampled infections that recover modeled transmission metrics. By comparing estimated metrics in modeled truth, she can derive genetic metrics that are most informative about malaria transmission to guide operational decision-making. Her findings suggest that simulated data provides a tool to understand how observations impact relationships between genetic and epidemiological metrics. Modelling can support the use of genomic data in productive ways to achieve elimination.

Joshua Suresh (Institute for Disease Modeling, Bill & Melinda Gates Foundation - BMGF, United States of America) investigated the impact of using primary schools to deliver intermittent preventive treatment to school-aged children (IPTsc) using mathematical models of transmission. Models were applied in Zambia, which represents a southern archetype, and Burkina Faso, representing a Sahel archetype. Their modeling found that IPTsc shows strong direct and community impact. An IPTsc strategy of presumptive treatment of all students with dihydroartemisinin-piperaquine (DP) once per school term reduces burden in school-age children by about 50%, and reduces the overall clinical burden in the community by about 30%, with the greatest community benefit found at the lowest transmission intensity. IPTsc outperforms increasing ITN coverage from 70% to 90%, which only reduces overall clinical burden by about 10%. This measure combined with standard seasonal chemoprevention (SMC) is less expensive and reduces more cases than SMC alone. He also presented important model factors which are not being evaluated including potential benefits like improved educational outcomes for school age children or potential risks like acceptability of frequent drug dosing to older children.

Branwen Owen (Swiss Tropical and Public Health Institute - Swiss TPH, Switzerland) aptly began with a call to be bold, highlighting the need to adapt interventions in order to reach new heights in the fight against malaria. Owen and team modeled data from an implementation trial that was conducted in Karamoja, Uganda. This trial used or planned to use five rounds of SMC in children less than five years old, from 2021 and 2022. Karamoja was considered suitable because of its high malaria prevalence, low bed-net coverage, single annual rainy season, and a mainly nomadic population. The model assumed 80% coverage at each of the five rounds, and predicted marked reduction in malaria incidence compared to a scenario of no SMC. Owen pointed out that the model shows a greater effect in incidence reduction when baseline incidence is low, and deviations to the plan are less important when malaria incidence is high. Therefore, it is vital to understand baseline incidence or prevalence at the site of, and to identify and eliminate likely impediments to maintaining coverage throughout SMC implementation. Owen, however, reminded the audience that a model can only be as accurate as its input parameters and assumptions.

S #93: Intermittent Preventive Treatment for Malaria in Infants with Sulfadoxine - Pyrimethamine (SP-IPTi): Fit for Purpose in 2021?

David Schellenberg (Global Malaria Program, WHO) chaired the session and gave a detailed background of how the SP-IPTi strategy was developed and the important factors influencing IPTi effectiveness such as access, coverage, incidence and drug efficacy. Professor Schellenberg highlighted that WHO recommended strategies should be tailored to fit each country's circumstances and that SP-IPTi was no different. Contact points for SP-IPTi can extend into the second year of life, and be delivered at any convenient health system touch point depending on the country specific setting.

Clara Menéndez (Barcelona Institute for Global Health - ISGlobal, Spain) began her presentation by giving a historical update on intermittent preventive treatment for malaria in infants (IPTi). The first

trial with IPTi using sulfadoxine-pyrimethamine (SP-IPTi) was conducted in 2001 in Ifakara, Tanzania. The positive results resulted in the creation of the IPTi Consortium with the support of Bill and Melinda Gates Foundation (BMGF) which analyzed the results of 6 randomised, placebo control trials in 8 different countries. The metanalaysis showed that SP-IPTi was effective against clinical malaria (30.3%) and anemia (21.3%) in addition to reducing hospital admissions with parasitemia (38 %) and all-cause admission (22.9%). In 2010 the World Health Organisation (WHO) recommended IPTi and recently these recommendations have been revised. However, to date, Sierra Leone is the only country that has implemented IPTi despite the challenges and barriers. Menedez later presented an overview of a new 40 months MULTIPLY project being implemented in Sierra Leone, Togo and Mozambique with the support of the Ministries of Health of African malaria endemic countries. This pilot implementation project MULTIPLY will expand SP-IPTi into the second year of life and will increase the uptake delivered along with the expanded immunization programme (EPI) mobile-outreach clinics. She concluded that it's high time to reconsider implementation of SP-IPTi in endemic countries and to overcome the already known health system barriers.

Dorothy Kah Fosah Achu (National Malaria Control Program - NMCP, Cameroon) presented the policy consideration for interventions for malaria in Cameroon. Malaria is a major public health problem in the country with increased incidence since 2016. The parasite accounts for 29.1% of outpatient visits, 40% hospitalizations, and 64% of deaths mostly among children. These findings inform that there is a need to target this vulnerable group with effective interventions. Control strategies adopted in the national strategic plan (NSP) 2019-2023 are preventive; through vector control, using long-lasting insecticidal nets (LLINs) given to children under-5 through EPI, chemoprevention using Intermittent preventive treatment for infant (IPTi-SP) with sulphadoxine-pyrimethamine; and case management through systematic diagnosis using RDT/microscopy and treatment of both uncomplicated and severe malaria cases in health facilities and via community case management. She then explained their rationale for including SP-IPTi in their NSP to reduce malaria morbidity and mortality in infants and children. With the goal of preventing malaria in vulnerable groups, they will implement SP-IPTp. However, attention should be given to cost-effectiveness, feasibility, equity of services, supplies and acceptability of SP-IPTi intervention.

Olusola Oresanya (Malaria Consortium, Nigeria) presented the context for the rationale of implementation research for SP-IPTi in Nigeria. Although Nigeria has witnessed a decline in malaria prevalence from 42% to 23% between 2010 and 2018, malaria remains a public health challenge by contributing 25% to the malaria global burden. Between 2013 and 2018, infant mortality rate only declined from 69% to 67%, thus flagging the need for more tailored intervention for this age group. SP-IPTi is currently not implemented in Nigeria, but an operational study (2020-2024) is part of the National Malaria Strategic Plan (NMSP) and will assess clinical effectiveness using cRCT (arm one SP-IPTi 3 doses; arm two SP-IPTi 5 doses; and arm three control with standard of care). It will also provide an opportunity to assess its operational feasibility using mixed-method study. She concluded her presentation by stating that evidence generated will inform policy formulation and adoption of the intervention by removing the bottlenecks.

Sian Clarke (London School of Hygiene and Tropical Medicine - LSHTM, United Kingdom) presented a co-creation design approach with the national stakeholders in the countries exploring the opportunities for adaptation of IPTi+ to fit country needs and SP resistance in sub-saharan africa. The project will be implemented and evaluated in 4 countries Ivory Coast, Benin, Cameroon and Mozambique; and later with more research and policy adoption in Ghana, Zambia and the Democratic Republic of the Congo. The + in IPTi, means to expand the number of doses given in IPTi, from three up to eight doses, and to widen the age range to be able to give the chemopreventive treatment during the second year of life. Countries will design their own strategy through a process called co-design. Model implementation for each specific country will be evaluated by research studies to

examine the process of implementation, impact achieved, cost and cost effectiveness. This will Inform countries on implementation, adaptation of IPTi in policy, and for World Health Organization development of guidelines. Clarke mentioned that they will also assess the effect of SP resistance by conducting cohort studies in Mozambique; evaluate the effect of different genotype mutations (including DHPS 581G mutation) in Cameroon and Zambia, and lastly genotyping surveys in countries of interest to determine subnational prevalence of genotype maps. Clarke concluded her talk by stating that findings from this project will help in development of a decision support tool for countries wanting to implement SP-IPTi+ and choosing the appropriate delivery strategy.

S #97: Malaria: Innovations in Malaria Prevention and Control

Baltazzar Candrinho (National Malaria Control Program - NMCP, Mozambique) started with an overview of the national malaria strategic plan in Mozambique between 2017 and 2022, and its recommendation of seasonal malaria chemoprevention (SMC) as a strategy to reduce malaria burden in high risk locations. In partnership with Malaria Consortium, the NMCP conducted an implementation study aiming at determining the protective effect of sulfadoxine-pyremethamine + amodiaquine (SPAQ) when used for SMC, and to assess the feasibility and accessibility of implementing SMC. The non-randomized controlled trial adopted a standard SMC implementation model commonly used in West and Central Africa. Candrinho reported that a high coverage of SMC knowledge, delivery and evidence of receipt of SPAQ was observed. Confirmed malaria cases during follow-up reduced significantly in intervention districts compared to control districts. Study also showed that SMC implementation using SPAQ is safe, feasible, and highly acceptable in the study areas. There was no report of serious adverse events. Parasite resistance to SP was high while resistance to AQ was low. He concluded by stating that the team's research plan for the second phase of the study.

Jimmy Anzolo (PATH, the Democratic Republic of the Congo) presented the Emergency Operations Centers (EOCs)-Malaria project. EOCs are used to follow emerging crises i.e. COVID-19. Anzolo described how PATH engaged with the Ministry of Health in the Democratic Republic of the Congo (DRC) to support its EOC's engagement to respond to COVID-19. The aim was to strengthen malaria burden reduction efforts while increasing the EOC's efficiency in responding to other emergencies. To reinforce the EOC's capacity to monitor multiple diseases, a dashboard was created. It now allows tracking morbidity and mortality data for COVID-19 and other diseases with epidemic potential. In the same approach, malaria dashboards were developed and are used by the National Malaria Control Program to monitor key indicators and cover existing malaria data sources and gaps. DRC malaria data served to calibrate a model to stratify malaria interventions. Predictive modeling helps outbreak detection, allowing a timely response. Anzolo also presented their training activities on malaria surveillance and management and the use of digital COVID-19 tracking tools. The next steps in this project aim to reinforce the use of data by the health system and to enable visualization down to the health area level; as well to continue enriching the dashboards using additional data sources.

Hillary Topazian (University of North Carolina at Chapel Hill, United States of America) discussed the effectiveness of a national mass distribution campaign of long-lasting insecticide-treated Nets (LLINs) and indoor residual spraying (IRS) on clinical malaria in Malawi during the period 2018-2020. Topazian started emphasizing that bed nets are the backbone of Malawi malaria interventions but neither its lifespan nor efficacy has been properly determined in field settings. Bed nets are distributed through massive campaigns every 3 years, and several insecticides are used. Topazian's group tried to determine how a mass distribution campaign of LLINs changes malaria risk over time. District Health Information Software 2 (DHIS2) data was used to determine the effect of LLIN type or annual application of IRS. After massive distribution of LLINs and IRS before high transmission seasons, malaria risk decreased from 25.6 to 16.7 cases per 100 people from 2018 to 2019, but rebounded to

23.2 in 2020, resulting in significant risk differences of -8.9 in 2019 and -2.4 in 2020 as compared to 2018. This shows that LLINs have a reduced efficacy lifespan once in the field; also, Piperonyl butoxide-treated (PBO) LLINs were more effective than pyrethroid-treated LLINs. DHIS2 probes to be a valuable source of information to follow malaria trends and to evaluate malaria trends and ongoing interventions.

Ann-Sophie Stratil (Malaria Consortium, Mozambique) commenced by stating that the outcome of two systematic assessments of Mozambique's surveillance system conducted in 2016-2018 identified the need for integrated Malaria Information Storage System (iMISS). Hence, the National Malaria Control Programme (NMCP) in partnership with other stakeholders initiated the development of iMISS. The primary goal of iMISS was to enable malaria staff at all levels of the health system to monitor key indicators, and to provide quality evidence to plan and implement responses. Stratil's study focused on evaluating the outcomes of the iMISS roll-out at the health facility level. Expected outcomes included data quality assessment, adoptability, acceptability, and maintenance issues during the first six months after roll-out. Quantitative and qualitative approaches were used to collect data using questionnaires and interviews. Findings indicated that iMISS is effective and well accepted. Data quality is sufficient, and the number of maintenance issues reported decreased over time. However, gaps were also identified. Technical issues need to be resolved while resolving the time of maintenance issues and adoption/data use needs improvement. She concluded by enumerating the next steps on integrating lessons learnt to allow the iMMIS reach its full potential before nationwide roll-out at the health facility level.

Adefisoye Adewole (African Field Epidemiology Network, Nigeria) presented the lessons learnt from the implementation of the Malaria Frontline Project (MFP) in the states of Zamfara and Kano in Nigeria between2016 and 2019. Adewole stated that poor data quality is a problem in all monitoring systems and limits decision making. A collaboration between the United States of America's Centers for Disease Control and Prevention (CDC) and the Nigeria National Malaria Elimination Program (NMEP) allowed the establishment of the Malaria Frontline Project. For capacity building, the strategy developed by the National Stop Transmission of Polio was applied. During the project, a local government area (LGA) supervisory team analyzed testing rate, clinical diagnosis and directly observed intermittent preventive treatment (IPTp) from the District Health Information Software 2 (DHIS2). Health facilities (HF) performing low in those indicators were visited more frequently, conducting on-the-job training and mentoring during visits. Adewole's group analyzed the reports of support visits to HFs from 2017 to 2019. During MFP, HFs testing rates increased and clinical diagnosis decreased. The proportion of HFs practicing the recommended directly observed IPTp increased. HFs analyzed the selected indicators from their malaria monitoring chart and used the results to make program decisions. DHIS2 data analysis helped HCWs at HF and LGA levels to improve malaria program performance.

Alassane Dicko (Malaria Research and Training Center, Mali) presented background information on seasonality of malaria and effectiveness of seasonal malaria chemoprevention (SMC). Despite the high efficacy of SMC, malaria continues to be a burden in Mali which is an indication of the need for additional intervention tools such as the malaria vaccine. The rationale for using the RTS,S malaria vaccine for seasonal vaccination was because of its high efficacy for a few months before it declined, and the possibility of restoring its efficacy with a booster vaccine. Alassane stated that their study was conducted among children 5-17 months old resident in Mali and Burkina Faso using a double-blind randomized control trial design. Morbidity data were collected continuously over 3 years through passive surveillance. Findings showed a very high vaccine and SMC coverage among the study groups throughout the period of study. The protection provided by seasonal RTS,S vaccination against clinical malaria was not inferior to the protection provided by 4 cycles of SMC per year. The addition of RTS,S

on top of SMC resulted in superior protection compared to the protection provided by SMC alone. And no major safety issue was recorded.

S #102: Ex Vivo Assessment of Drug Susceptibility of the Antimalarial Drug Pipeline

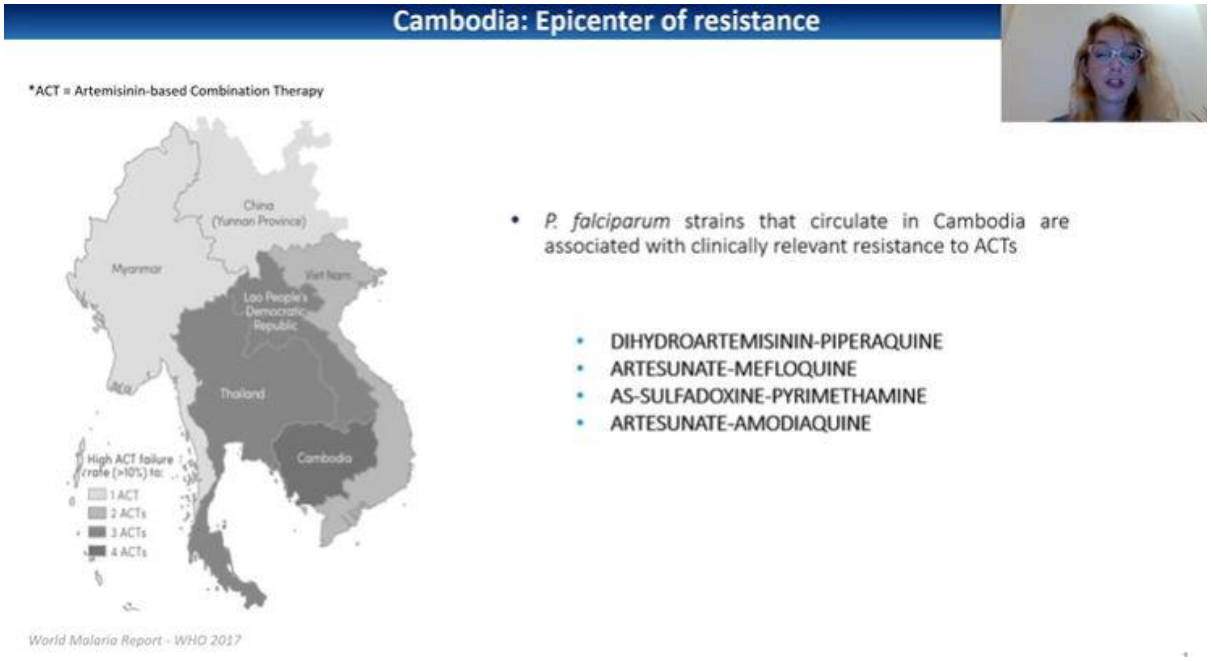
Oriana Kreutzfeld (University of California, United States of America) presented work on the efficacy of antimalarials (exploratory and advanced compounds) on fresh clinical isolates from Tororo and Busia Districts in eastern Uganda from 2016 to 2020. The long and ongoing study was done to evaluate the full Medicines for Malaria Venture (MMV) pipeline and identify genomic markers associated with decreased susceptibility to newly developed inhibitors. Fresh isolates from the patients diagnosed with *Plasmodium falciparum (Pf)* infection were collected and blotted on filter paper for genotypic analysis. Ex vivo drug susceptibility studies were done on samples with parasitaemia greater than 1%. She reported parasites being highly susceptible to most of the 40 MMV pipeline inhibitors; similar results were seen in a newer study done in Bobo-Dioulasso, Burkina Faso. PfATP inhibitors were highly active against Uganda *Pf* isolates. Isolates with the G223S mutation had decreased susceptibility to PfATP inhibitors, but differences were modest. Older PfDHR inhibitors (pyrimethamine and cycloguanil) had reduced activity against Ugandan *Pf* isolates with multiple PfDHFR mutations, whereas a 2, 4 – diaminopyrimidine (P218) was highly active. Surprisingly, 16% of isolates carried the quadruple 51I/59R/108N/164L DHFR mutation, which had decreased susceptibility to pyrimethamine, cycloguanil and P218, although P218 retained excellent activity.

Laurent Dembelé (Malaria Research and Training Center of Bamako, Mali) presented work on the characterization of ex vivo malaria parasite drug susceptibility in Ghana and Mali. He developed an ex vivo assay to test drug activity against *Plasmodium falciparum (Pf*), *malariae (Pm), ovale (Po),* and *vivax (Pv)* species, while a polymerase chain reaction assay was used to confirm the species identified. Using fresh isolates from a pilot study, the activity of a reference drug was established. In Mali, *Pf* was the most predominant species, while *Pm* accounted for 15% of the infections. He reported a similar trend in Ghana, where *Pm* was the second most prominent amongst the 22% non-*Pf* infections. A decreased susceptibility of *Pm* isolates to artemether, lumefantrine and chloroquine was observed compared to *Pf*, but no differences in susceptibility to artesunate, lumefantrine, chloroquine, quinine and pyrimethamine were observed in *Po*. Piperaquine was found to be a potent inhibitor of *Pm* and *Pf* isolates. Furthermore, all species were susceptible to novel candidate antimalarial drugs – KDU691 and GNF179 – with no significant differences among the species in Ghana and Mali. He suggested further research to be done to assess the efficacy of artemisinin combination therapies and other drugs against *Pm* infections.

Camille Roesch (Institut Pasteur in Cambodia) presented on profiling new antimalarials against Cambodian parasites. *Pf* strains in Cambodia are associated with clinically relevant resistance to ACTs. Parasites in South-East Asia are polymorphic and versatile so it's crucial to screen new molecules against representative strains that are circulating. Currently, there are two major profiles of resistance detected in Cambodia: MQ-R and PQ-R. For sustainable malaria control, they proposed a triple combination therapy, although triple resistance may exist. Within their strains and molecules tested, four out of nine drug candidates would be accepted because they had similar IC50's among all genotypes and their activity was not associated with pre-existing resistance patterns. Another four molecules would be rejected because their IC50's were associated with preexisting resistance patterns. Ongoing work includes whole genome sequencing of isolates with phenotypes of interest.

Caroline Aguiar (University of Sao Paulo, Brazil) talked about ex vivo assessment of drug susceptibility of the antimalarial drug pipeline against Pf and Pv using a novel schizont maturation assay. To analyze, they counted the number of schizonts and compared results with those from non-treated controls. They tested over 100 compounds using the schizont maturation assay against *Pv* and *Pf*. Importantly,

no significant differences in susceptibility between Pf and Pf were observed for the antimalarial used in the field (lumefantrine, chloroquine, mefloquine, artesunate, pyronaridine, atovaquone, piperaquine and amodiaquine). A good correlation was found between IC50 for *Pf* and *Pv* field isolates, showing that most compounds that are active against *Pf* are also active against *Pv* parasites.



S #113: Genetic Approaches to Elucidating *Plasmodium Falciparum* Antimalarial Modes of Action, Drug Resistance and Fitness

Sachel Mok (Columbia University Irving Medical Center, United States of America) discussed a study titled, "Mapping antimalarial drug resistance determinants using *P. falciparum* genetic crosses in humanized mice". The presentation focused on phenotypic, genetic and genomic analyses that have mapped determinants of parasite resistance to multiple antimalarials such as artemisinin, piperaquine, chloroquine and quinine, using contemporary drug-resistant clinical isolates obtained from Southeast Asia crossed with the African NF54 strain. Her findings provide compelling evidence that the *k13* gene is the primary mediator of ring-stage parasite resistance to artemisinin derivatives and suggest the presence of secondary determinants that might modulate survival rates among the *k13* mutants. Also, piperaquine was observed to select for the Southeast Asian KeI1/Pla1 co-lineage. Forward and reverse genetic studies highlighted an epistatic interaction between the *Pf* chloroquine resistance transporter (PfCRT) Dd2+M343L variant and plasmepsin II gene amplification in contributing to piperaquine resistance. This group also identified the drug metabolite transporter (DMT1) as a new potential marker for quinine resistance. Overall, the studies showed that quantitative trait locus (QTL) mapping can identify loci involving drug resistance, which may influence the parasite's fitness during resistance acquisition. Finally, her data showed that genetic crosses are a useful tool for teasing out drug resistance mechanisms, including for drugs with unknown modes of resistance or action, through the use of bulk segregant analysis (BSA) and clone-based linkage mapping.

Ashley Vaughan (Seattle Children's Research Institute, United States of America) discussed the leveraging of *Plasmodium falciparum* genetic crosses to understand fitness and life cycle progression. *P. falciparum* genetic crosses are now routinely carried out in the lab and along with collaborators, six unique crosses with multiple biological replicates spanning eight parental parasites have been conducted over the last four years. The team is using bulk segregant analysis (BSA) to

understand nutritional genomics by comparing the growth of recombinant parasite populations in different media formulations in long-term competitive fitness experiments. *In vitro P. falciparum* cultures often use AlbuMax as a lipid substitute for human serum, however, the impact of using the latter on parasite growth and drug sensitivity is poorly understood. Analysis of genome inheritance over time in serum versus AlbuMax revealed strong genomic skews on chromosome 13, in a segment containing erythrocyte binding antigen 140 (EBA-140), suggesting that redundant invasion pathways used by parasites are dependent on the nutritional status of the media. Further work will determine the relevance of these studies to the *in vivo* condition. The team has also used BSA in combination with classical genetics to show that mutations in the amino acid transporter *pfaat1* are linked to resistance to the antimalarial chloroquine and mutations in the chloroquine resistance transporter *pfcrt*.

Marcus Lee (Wellcome Sanger Institute, United Kingdom) presented a study that focused on the use of barcoding technology to define parasite resistance to experimental antimalarials that are being explored for future drug discovery research. There is a need to develop new drugs that are not subject to existing resistance mechanisms. To achieve this, a relatively high proportion of *Plasmodium* genes are required for normal growth, which suggests many potential drug targets remain to be associated with chemical inhibitors. The study utilized resistant parasite lines generated by the Bill & Melinda Gates Foundation-funded Malaria Drug Accelerator (MalDA) consortium that aims to identify new drug targets, understand modes of action and generate early lead inhibitors. Resistant lines were barcoded by CRISPR, allowing multiple lines to be pooled and grown in competition. Barcode sequencing of the parasite pool can reveal fitness and drug response phenotypes. Fitness assays measured growth over 60 days and revealed a range of fitness costs for different mutants. In addition, short term drug exposure of the pool allowed rapid target identification by detection of enriched barcodes. Barcode enrichment is reproducible and the assay can also be configured to detect hypersensitivity of specific mutants to test compounds.

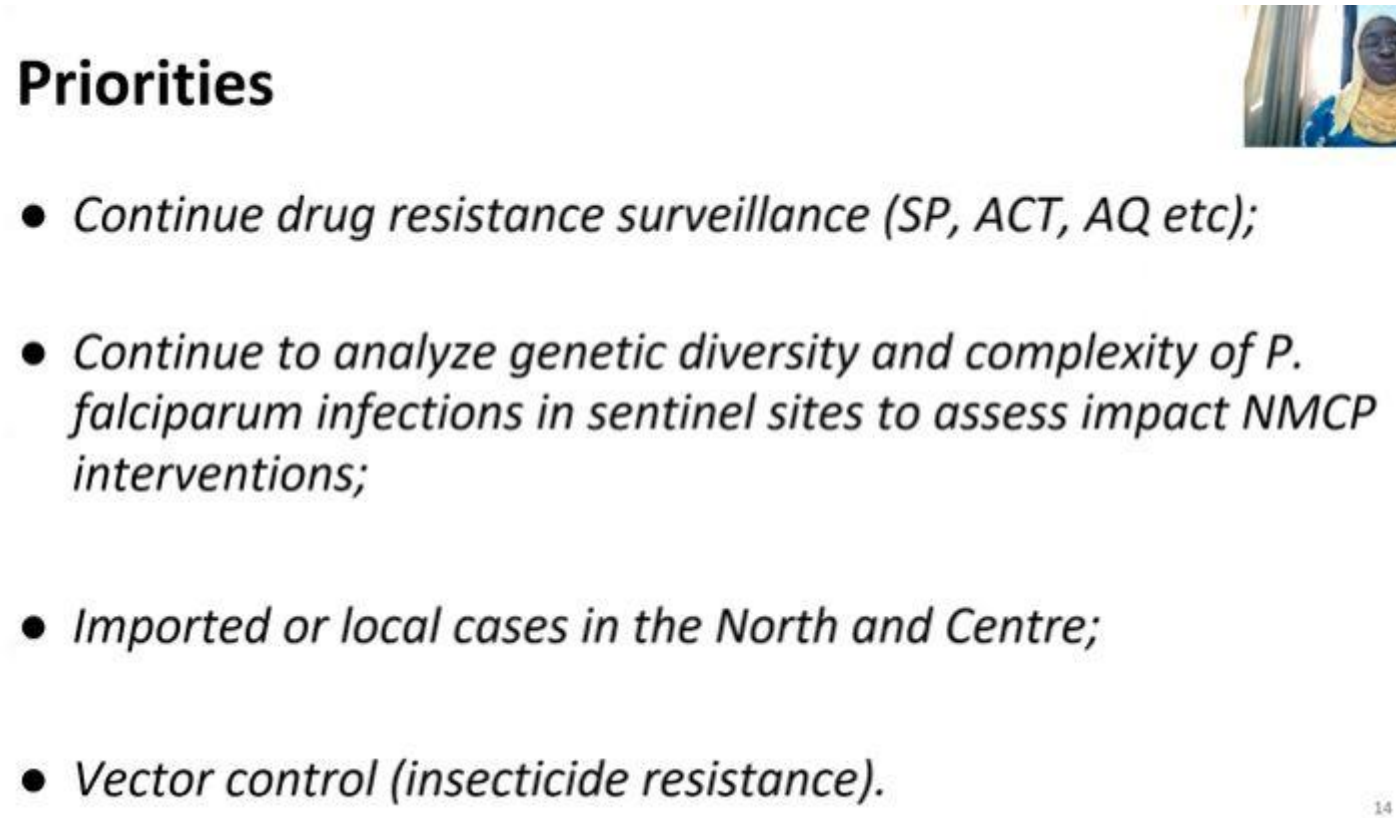
Charisse Flerida Pasaje (Massachusetts Institute of Technology, United States of America) showcased how she utilized conditional gene down-regulation studies and developed a cell-based differential sensitivity phenotypic platform to inform antimalarial drug discovery by validating compound-target interactions and screening for inhibitors of an essential protein. To expand on her work, she reported on a number of applications that were carried out as part of the MalDA consortium by demonstrating the ability of the platform to validate inhibitors of the cytosolic isoleucyl-tRNA synthetase, the cGMP-dependent protein kinase PKG, and the bifunctional farnesyltransferase/ geranylgeraniol pyrophosphate synthase (GGPPS). Additionally, she showed the specificity of the technology to pick up compound-target pairs when screening against panel conditional knockdown lines. Key concluding points in her presentation were that conditional knockdown systems allow for efficient and accurate mapping of target-compound interactions, and can confirm or reject resistance mechanisms that emerge from various target identification pipelines.

This report is brought to you by the MESA Correspondents Edima Ottoho, Tope Kayode, Franklin Tembongshu Formilack, Lucy W. Mwangi, Vita Mithi, Ana Alonso, Faith Hungwe, Olajoju Temidayo Soniran, Isabelle Delrieu, Doumbe Belisse Patricia and Carlos A. Fernández Miñope, with mentoring and editorial support from Divya Beri.

Day 5: 21th November 2021

S #119: Integrating Molecular Data into Malaria Surveillance: Progress in Senegal

Fatou Ba Fall (National Malaria Control Program - NMCP, Senegal) presented the progress and challenges toward integration of molecular epidemiology data into the decision making process by the NMCP. Senegal's National Strategic Plan 2021-2025 aims to reduce transmission by at least 75%. Through epidemiological profile analysis, 3 zones were selected and stratified by transmission level. Surveillance was conducted to follow the evolution of the disease in time. Since 2001, malaria mortality and morbidity has reduced by ~30%, reaching 3.81% proportional morbidity in 2020. Low levels are now an issue and hard to manage by malaria surveillance. Senegal aims now to eliminate malaria by 2030. Genomic data can have an important role in surveillance, allowing to reorient and better select interventions and priorities. This included the genetic surveillance of drug resistance markers (PfCRT-76T, PfMDR-86Y, PfMDRTT-184F) of importance for the first line of antimalarial treatment. Genetic information helped to differentiate between local and imported infections; also, revealed transmission patterns. Ba Fall stated at the end that in fact, this information has been used in the decision making by NMCP.



July Thwing (Centers for Disease Control and Prevention - CDC, United States of America) in her talk developed diverse ways to design sampling strategies in health facilities and community levels. At health posts, blood samples and positive rapid diagnostic tests (RDTs) samples were collected in sites of interest to the National Malaria Control Program of Senegal. At community level, she reported that sampling was performed in three sites Sessene, Ndoga Babacar and Kedougou. Besides, a cross sectional survey was performed in schools and a proactive model in which community health workers (CHWs) visited all households, known as PECADOM plus platform "Prise en charge du paludisme à domicile'', was deployed. Thwing emphasized the importance of this system and the opportunity to use it as a surveillance tool to measure impact. PECADOM mainly focused on household weekly visits to identify fever cases, offer RDTs and treat positives, and on the other hand on the collection of filter

paper samples and basic demographic data. She highlighted at the end that those sampling frameworks help them to get malaria transmission dynamics, seasonal transitions and population seroprevalence, important metrics for basic surveillance.

Aida Badiane (University Cheikh Anta Diop, Senegal) talked about epidemiological measures of infectious disease with a great focus on serosurveillance through multiplex serology. She started by explaining the interests of epidemiological measures, they are the foundation to monitor diseases, formulate and evaluate healthcare policy, and conduct scientific research. She deeply explained the importance of serosurveillance in the detection of malaria exposure over time to understand disease burden and to measure change when malaria incidence and prevalence are low. Badiane talked about a relevant advantage of serosurveillance through multiplex serology, which can detect and quantify dozens of antigens simultaneously. Then, she also presented some ways to implement serosurveillance like community-based cross sectional surveys or a survey in a sentinel site. She also reported results from a survey performed in 24 sentinel sites by the NMCP of Senegal. Results show two types of antibodies PfMSP-1 and LSA-1 which could be categorised by age group and area. She concluded by stating some things to be considered for sustainability of serosurveillance like maintenance of skills, maintenance of equipment and procurement of reagents.

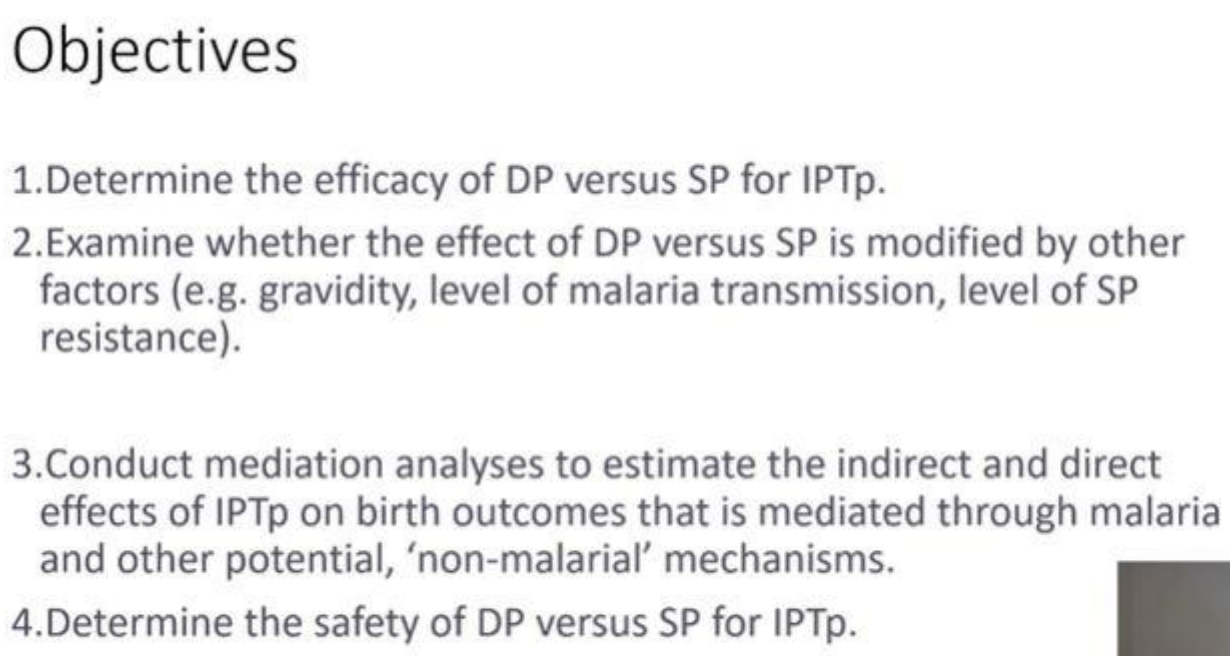
At the onset of her talk, **Caitlin Bever** (Institute for Disease Modeling - IDMOD, United States of America) presented different models to show that models help to take information available and turn it into actionable information. It helps to unify the framework for understanding diverse field observations. Bever then reflected that a very relevant and well-known country-led approach to malaria program decision-making known as high burden to high impact (HBHI) is supported by different models that assess different data. She also highlighted that there is a need to assess the constant impact of interventions and also the role of malaria imported cases in sustaining malaria transmission in different regions. Bever reminded the attendees that to use models, we have to define data of interest and types of data in advance and that a model informs you of how to collect efficient and informative data in programmatic mode.

S # 125: Dihydroartemisinin-piperaquine as an Alternative Drug for Intermittent Preventive Treatment for the Control of Malaria in Pregnancy in Areas of High Sulphadoxine-Pyrimethamine Resistance in East and Southern Africa

WHO recommends intermittent preventive treatment (IPTp) with sulphadoxine-pyrimethamine (SP) for preventing malaria in pregnancy, but high-level SP resistance threatens its efficacy in parts of East and Southern Africa. **Mwayiwawo Madanitsa** (University of Malawi, Malawi) presented the findings of a randomized trial that compared the efficacy of IPTp with sulphadoxine-pyrimethamine (SP) versus dihydroartemisinin-piperaquine (DP) with or without azithromycin (AZ) in reducing adverse pregnancy outcomes in Kenya, Malawi & Tanzania. He commenced by reporting alternative prevention strategies tested (between 2007 and 2019) amongst which only DP was promising compared to SP. Madanitsa's study was a multi-center, 3- arm (monthly SP, monthly DP, and monthly DP + AZ), a parallel trial conducted from 2018 to 2021. 4680 women were enrolled, administered a monthly treatment, and followed up to 8 weeks postpartum. Both DP arms performed worse than SP at preventing adverse pregnancy outcomes. The beneficial effects of SP were driven by better fetal growth resulting in fewer low birth weight newborns. There was no difference in preterm delivery, fetal loss, and neonatal death across all arms. DP significantly reduced malaria relative to SP. He recommended that DP should not replace SP as IPTp even in areas with high SP resistance.

Feiko ter Kuile (Liverpool School of Tropical Medicine, United Kingdom) presented a meta-analysis that compared intermittent preventive treatment (IPTp) with dihydroartemisinin-piperaquine (DP) versus sulphadoxine-pyrimethamine (SP) for the prevention of malaria in pregnancy and adverse

pregnancy outcomes in Kenya, Malawi, Tanzania, and Uganda. The study aimed to provide definitive evidence for WHO's policymaking. Eight data sets (with a combined 6687 pregnancies) were pooled from six trials. The 6687 pregnancies were separated into two arms – DP and SP - based on the IPTp taken. Clinical malaria, placental malaria, and malaria at delivery were lower in the DP arm. DP was not superior to SP in preventing adverse pregnancy outcomes (fetal loss, low birthweight, preterm delivery, neonatal death) in the different gravidae groups. However, small for gestational age was less frequent in the SP arm and birthweight-for-gestational age z-scores were higher in the SP arm. Birthweight was 49g higher in the SP arm, possibly reflecting better gestational weight gain (GWG) per week in this arm. Dr. Ter Kuile suggested that future studies should explore the antimalarial activity of DP and the non-malarial effects of SP in a DP + SP combination.



The study presented by **Michelle Roh** (University of California San Francisco (UCSF), United States of America) aimed to break down the antimalarial and non-malarial effects of IPTp drugs on birth weight, and to quantify the effect of Sulphadoxine-Pyrimethamine (SP) on gestational weight gain (GWG) contributing towards birth weight. Mediation analysis is an epidemiological method that quantifies the extent to which an intermediate variable influences the effect of an exposure on an outcome. Roh and her team conducted mediation analyses using data from 6603 pregnant women included in a meta-analysis resulting in live births. Her results showed that despite its greater effect on malaria prevention, DP appears to only have a slightly greater antimalarial benefit on birthweight, though this effect may vary by malaria transmission setting. Consistent with Roh's previous mediation analyses of 3 studies, SP appears to exhibit non-malarial benefits on birth weight, and this may be due, in part, to SP's greater effect on GWG. Sensitivity analyses will be conducted to rule out bias due to potential unmeasured confounding and mismeasurement of the mediator. Furthermore, more sophisticated mediation analyses will allow assessment of the independent contribution of factors in mediating the SP and birth outcome pathway, using longitudinal measurements of malaria and gestational weight gain. Future studies will focus on assessing effect modifiers that may explain the heterogeneity in the overall and mediated effects.

Concerns about Sulphadoxine-Pyrimethamine (SP) resistance have led to trials exploring repeated treatment courses of dihydroartemisinin-piperaquine (DP) as an alternative for malaria

chemoprevention. However, piperaquine is associated with dose-dependent prolongation of the cardiac QT interval that may lead to increased risk of serious arrhythmia and Torsades de Pointes. **Julie Gutman** (Centers for Disease Control and Prevention, United States of America), presented an individual participant data meta-analysis on the cardiotoxicity of dihydroartemisinin-piperaquine (DP) when used for IPTp for the prevention of malaria in pregnancy. Repeated doses of DP were found to be safe. Study specific correction of the QT provided the best adjustment for heart rate. Prolongation of the QT interval greater than 480 ms was infrequent and prolongation greater than 500 ms was rare. Corrected QT (QTc) prolongation occurred most frequently after the initial course, with fewer individuals exhibiting extreme QTc prolongation with subsequent courses, suggesting a tolerance mechanism, and highlighting that repeater courses are not associated with an increased risk for QTc prolongation.

S #130: Expanding the Use of Safe and Effective Radical Cure of Relapsing Malaria: Defining Populations at Risk of Hemolysis

Ari Winasti Satyagraha (Eijkman Institute for Molecular Biology, Indonesia) spoke about glucose-6-phosphate dehydrogenase (G6PD), an X-linked gene known for its antioxidant activity in erythrocytes. G6PD deficient individuals may develop acute haemolytic anaemia when exposed to oxidative malarial drugs like primaquine/tafenoquine. G6PD phenotypic expression in females is varied (low: <30% of normal activity, usually calculated as the Adjusted Male Median; intermediate: 30-70% of AMM; normal: >70%of AMM). In this study, Satyagraha's aim was to determine the degree of haemolysis in the intermediate female G6PD activity cohort who are capable of haemolysing. In another study, they evaluated malondialdehyde (MDA) and glutathione (GSH) levels to determine the extent of membrane damage caused by oxidative stress. A Carestart Biosensor quantitative assay was conducted and it was found that most females who were primarily infected with *Plasmodium falciparum (Pf)* were located in the middle of the histogram. These results enabled Satyagraha to determine the population's minimum G6PD activity threshold for counteracting oxidative stress, that is, females who are capable of undergoing primaquine/tafenoquine therapy. MDA and GSH results showed that higher G6PD activity does provide increased protection against oxidation. More MDA and GSH work still needs to be conducted on intermediate G6PD activity female cohorts to better understand the pharmacokinetics.

Benedikt Ley (Menzies School of Health Research and Charles Darwin University, Australia) spoke of how 8-aminoquinolines drugs effectively remove hypnozoites from the liver but are not often prescribed because they cause severe drug induced haemolysis in G6PD deficient (G6PDd) patients. The aim of this study was to assess whether G6PD activity increased during plasmodium infection. They used study results from studies conducted in Bangladesh in the last seven years. Ley compared G6PD activity between a treatment efficacy survey (G6PD participants with malaria) and a cross-sectional survey (G6PD participants with no malaria). In addition, they conducted a case control study that enrolled G6PDd participants (with no history of malaria versus history of malaria) to quantify the potential protective effect of G6PD deficiency against malaria which would affect the outcome of the former comparison. The clinical trial aimed at evaluating the efficacy of national treatment guidelines whilst the cross-sectional survey assessed G6PDd prevalence in the local population. A mixed method approach was used and found that G6PD activity significantly differed between participants with and without malaria infection. However, no significant difference between aparasitemic and sub-microscopic participants was observed but Ley believed that had a clinical relevance. He concluded his talk by stating the limitations of the study that it did not factor G6PD activity change over time. This could be rectified in a more incorporative longitudinal study.

James Watson (Mahidol Oxford Tropical Medicine Research Unit, Bangkok) talk was on determinants of hemolysis following primaquine administration in G6PD deficiency. He pointed out that hemolysis

in G6PD deficiency is determined by multiple factors; dose of primaquine, exposure to the primaquine metabolites, G6PD mutation, disease effect in malaria vs. healthy volunteers and red cell age distribution. Watson outlined that G6PD deficiency reflects an unstable enzyme that has the tendency of degrading rapidly; functional enzyme activity in reticulocytes is higher than in mature erythrocytes, and older cells hemolyze first. The presentation focused on the age distribution of the red cells in individuals given primaquine and how this determines the existence of hemolysis in a clinical trial using data of healthy volunteers that were G6PD deficient, in ascending primaquine dosing of healthy males. Participants were given regimes between 15 and 20 days with the smallest dosing of 7.5mg and the largest dosing of 45mg. They recorded daily hemoglobin, and applied rules on safety and monitoring of clinical symptoms of participants throughout the trial. In the second half of the trial, a total dose of 5-8 mg/kg was given for 15 days. The results showed a 25% - 33% decrease in hemoglobin. However, dose escalation was stopped in 1 symptomatic person because there was more than 30% drop. Decline in hemoglobin was dependent on the rate of primaquine escalation and hemoglobin initiation. However, for *P. vivax* malaria, the hemolysis is seen after admission and following treatment is due to disease and not the drug. In conclusion, the degree of hemolysis in G6PD deficiency is dependent on red cell age distribution.

Cindy Chu (Shoklo Malaria Research Unit, Thailand) presented the overview of data to date on clinical hemolysis caused by 8-aminquinoline. She emphasized the degree of clinical haemolysis and associated phenotypes in addition to the G6PD activity phenotype. Early research done in the 1950-70s focused on the clinical aspect of hemoglobin drops, and dose dependent primaquine related hemolysis. These early trials also observed that hemolysis was most common in some adversities. In the 1970-80s, focus shifted to the characterisation of the G6PD genotype and phenotype. Today the genetic data has not been analyzed together with the G6PD phenotype or clinical hemolysis, and it is even rare to combine all three aspects. This forms a research gap that needs to be breached. Chu urged clinicians to pay more attention to haemoglobin recovery and advocating for a revised version of the WHO classification of mutation based on risk assessment of clinical haemolysis. The revised classification will assist in providing more accurate clinical data. Chu concluded her talk by reiterating the importance of conducting work aimed at reclassifying haemolytic drugs whilst considering the factors involved in haemolysis and haemolysis recovery.

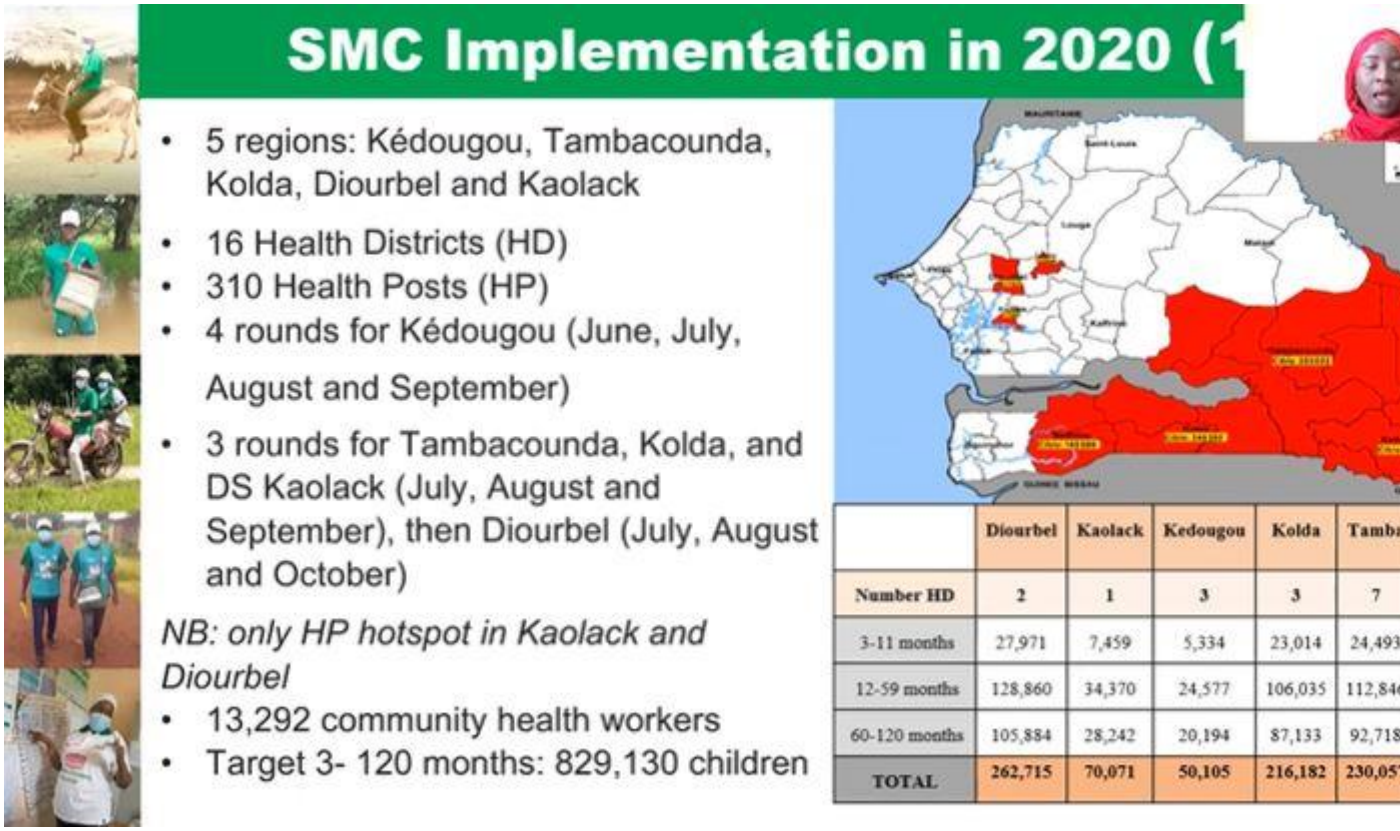
S #136: Implementing Malaria Chemoprevention Campaigns During the COVID-19 Pandemic

Abimbola Phillips (Malaria Consortium - MC, Nigeria) started his talk by explaining that MC provided community distributors (CDs) to deliver seasonal malaria chemoprevention (SMC) door-to-door in the midst of COVID-19 pandemic increasing the risk of infection. Then they conducted a cross-sectional study in Kano and Sokoto States to assess CDs' adherence to the infection prevention control (IPC) guidelines developed by MC. Findings showed a greater availability of IPC equipment for SMC in Sokoto than in Kano. For adherence to IPC practices, in Kano, practice of hand hygiene for at least 30 seconds occurred at only 0.7% of 1503 possible opportunities, while in Sokoto, it occurred at 3.6% of 1578 possible opportunities. There was no disinfection of sulfadoxine-pyrimethamine (SP) together with amodiaquine (AQ) blisters, nor safe disposal of masks/wipes at any instance in Kano, but in Sokoto. Masks were used 62% of possible times in Kano, but 74% in Sokoto. CDs maintained safe distancing at 5.1% of times in Kano but 16% in Sokoto. Adherence variance among CDs, influenced by equipment availability, training on procedures, community members' reactions and difficulty in keeping appropriate physical distance. Adequate knowledge, CDs' positive perceptions of the IPC measures and feasibility of implementation were adherence drivers.

Assane Kano (Catholic Relief Services - CRS, Niger) presented a study on the integration of SMC and malnutrition screening in Niger, prior to and during the COVID-19 pandemic based on an analysis of routine data collected since 2016. He explained that CRS is a principal recipient of a 3-year Global Fund

project, with the goal of 40% malaria morbidity and mortality reduction in 8 regions and 72 health districts, and one of its key interventions is SMC. He explained that SMC has evolved over the years from 12-17 health districts coverage and stand-alone campaigns in 2013-2015 to 28-61 health districts, and integrated campaigns in 2016-2021, with increased partners' funding/support. Also, a door-to-door approach was adopted over the previous fixed sites SMC and malnutrition campaign approach since COVID-19 hit Niger in March, 2020, resulting in an increase in SMC annual target from 205,959 to 4,289,520; and coverage from 86% to 105% from 2016 to 2020 respectively. Similarly, malnutrition intervention, since its integration with SMC, has improved annual coverage from 54% in 2016 to 109% in 2020 because Community distributors now reach more targeted children in their homes.

Seynabou Gaye (National Malaria Control Program - NMCP, Senegal) presented findings from a study titled, 'Implementing Directly Observed Treatments for Three days (DOTS3) for SMC during the COVID-19 pandemic in Senegal'. They implemented SMC in 5 regions in Senegal, adopted a mass campaign approach, used community volunteers and administered 3 to 4 treatment passages of SP + AQ at monthly intervals. There was a theoretical coverage of 85.8% of children aged 3-120 months, of which 96.3% received the 3rd dose of CPS. There was an overall achievement of SMC goals, stakeholders were trained and developed a memorandum on the prevention rules COVID-19 during the SMC campaign. They made sure to warn of side effects early using the 3-day direct observational treatment (DOT) approach. In the end, Gaye stated how crucial was the support and involvement of partners in the implementation, including health committees and local authorities.



	Diourbel	Kaolack	Kedougou	Kolda	Tamba
Number HD	2	1	3	3	7
3-11 months	27,971	7,459	5,334	23,014	24,493
12-59 months	128,860	34,370	24,577	106,035	112,84
60-120 months	105,884	28,242	20,194	87,133	92,718
TOTAL	262,715	70,071	50,105	216,182	230,05

Pedro Aide (Manhica Health Research Center - CISM, Mozambique) presented results from a malaria mass drug administration (MDA) amongst displaced populations in the province of Cabo Delgado in Mozambique. The objective of the MDA was to reduce the burden on health services through the reduction in malaria transmission, morbidity and mortality, even though public health had been

weakened by population growth resulting from migration to relatively safe regions. For all the eligible population, 3 rounds of MDA were given, aiming to cover the entire malaria transmission season: february, april until the end of May. They used a door-to-door implementation strategy and a scanning strategy to reach most households in the village before moving on to the next village. They found the need for a strategy of triangulating data from different sources before the start of each round including information from village leads about population movements. More support staff was needed beyond district personnel, both in terms of fieldworkers and coordinators. Aide concluded by highlighting some key messages MDA was successfully delivered in a challenging environment, coverage was improved between the different rounds of MDA, campaigns managed to avoid an expected increase in malaria cases, and both communities and internally displaced people (IDP) camps benefited from the campaign.

S #140: Eliminating Malaria in the Guiana Shield During COVID-19 Times: How Can We Accelerate It?

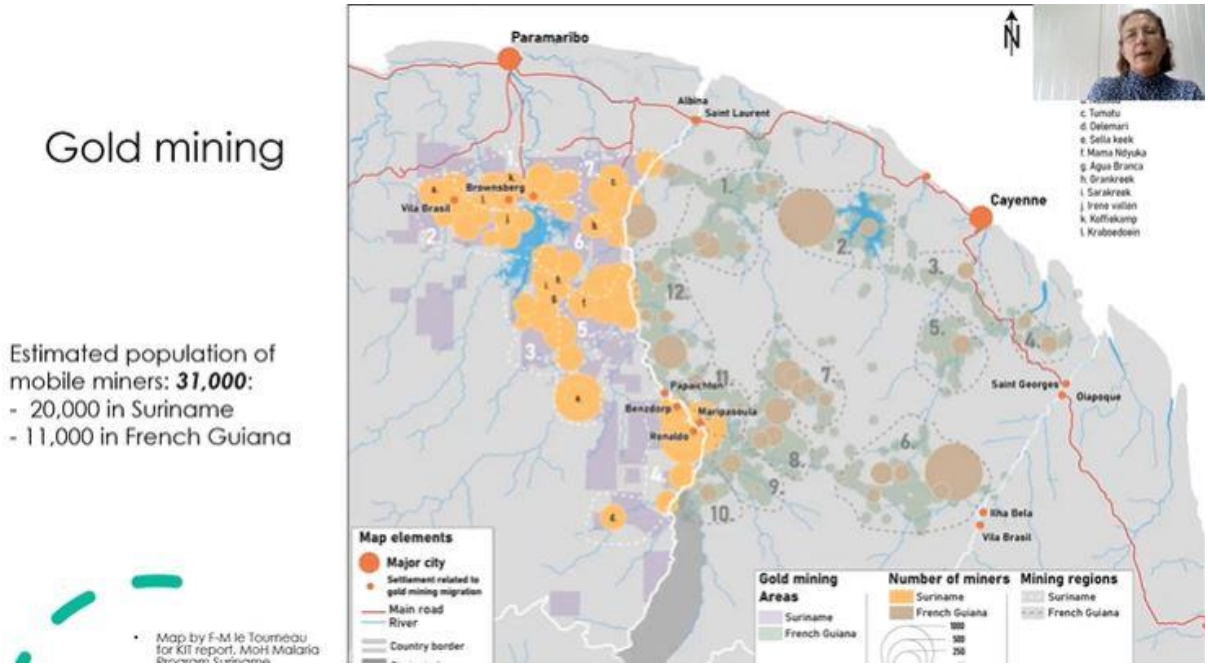
Introductory remarks by **Leopoldo Villegas** (ASOCIS, Venezuela) outlined the uniqueness of the Guiana Shield. Geographically, the Guiana Shield underlies Venezuela, Guyana, Suriname and French Guiana as well as parts of Colombia and Brazil and is home to numerous minerals, majorly gold. This region, he went on to explain, is responsible for most of the malaria transmission in South America, mainly due to malaria importation from the mining areas to the hinterland; as well as some of the most multi-drug resistant malaria parasites. Nonetheless, Villegas noted that there have been significant strides in malaria in the region especially over the last decade as there has been concerted efforts made in countries on both extremes of the malaria spectrum that is the malaria-free to high transmission areas; however mobile and hard-to-reach populations remain the most important and affected groups.

Guyana, a country with about 750,000 inhabitants with limited access to care, sees about 20,000 cases of malaria per year, majority caused by *P. vivax (Pv)*, some by *P. falciparum (Pf)* and a little by *P. malariae*. In 2020, 76% of the infections in the hinterland were due to migration to areas of gold mining and logging for economic benefit. Then **Horace Cox** (Ministry of Health, Guyana) discussed the lessons from malaria diagnosis, treatment and elimination in sentinel sites. Therapeutic efficacy studies (TES) in 2014 revealed Pf K13 mutations indicating parasite resistance to artemether-lumefantrine (AL); while in 2019 AL was found an efficacious treatment and no mutations were detected. Though microscopy was the standard mode for routine malaria diagnosis, rapid diagnostic tests (RDTs) were used to supplement testing while polymerase chain reaction (PCR) was employed in this study. Interestingly, Cox observed an increase in slide positivity rate, yet the number of tests done decreased. He emphasised that innovation is needed to accelerate testing, ensure universal access to diagnosis and treatment, and expand surveillance. Further, the relationship between human behaviour, risk perception and knowledge was assessed observing that risk did not drive human behaviour, and knowledge influenced behaviour more than perception. Aside from migration to mining camps, other factors contributed to malaria transmission, including seasonality and the price of gold. With respect to mosquito capture methods, the Shannon modified trap was found to be the best. In addition, Cox stated the importance of studying parasite genetics for a better understanding of mutations, host-parasite interactions and therapeutic efficacy. In conclusion, Cox outlined four pillars for malaria elimination learned through their study as: (i) ensuring universal access to vector control; (ii) ensuring universal access to case management; (iii) transforming surveillance systems and (iv) collaboration to create tailored interventions and illustrative as well as educational materials for malaria prevention.

Lise Musset (Institut Pasteur de la Guyana, French Guiana) started her presentation with a descriptive narrative on geographical location of French Guiana, population, shared context with neighboring

countries and its impact on malaria transmission. In the past decade, malaria cases caused by *P. falciparum* and *P. vivax* reduced greatly but *Pv* cases increased slightly in 2016. Interestingly, she noted that no malaria mortality was recorded since 2013, but in 2020 only 4 cases of *Pf* malaria were recorded out of which 2 were imported cases. Musset stated that these results were achieved due to implementation of interventions which included new drugs and accelerated deployment of rapid diagnostic tests from 2007 to 2010; community approach in neighboring countries in 2009; some operational research programs on better malaria control conducted between 2015 and 2019; and military operation against illegal gold mining. One of the programs implemented was the Resistance and Emergence to Artemisinin and its partner drugs in the Guiana Shield to Identify them to better Restrain (REAGIR), whose findings showed that artemether-lumefantrine was still efficacious, and identified two malaria transmission hotspots. Another was PALUSTOP which employed active case detection by PCR followed by systematic treatment of positive cases. Musset also emphasised the importance of collaboration through which the MALAKIT project was implemented. In the end, she highlighted main drivers for malaria transmission as (i) living in a remote area close to the forest, (ii) occupational activities such as gold mining, agriculture and hunting, (iii) having poor knowledge regarding malaria, and (iv) *Pv* transmission.

Helene Hiwat (Ministry of Health, Suriname) commenced with a brief description of the Republic of Suriname, noting that in the coast there is no malaria but in the interior region malaria transmission is still taking place. She briefly highlighted the history of malaria in Suriname stating the changing malaria epidemiology due to mining activities and cross-border movement of gold mining populations from French Guiana. Hiwat noted that since 2018 low malaria incidence was observed in the country with some re-introduction of *Pv* malaria, but these outbreaks had been contained since August 2021. Unfortunately, re-introduction of *P. vivax* had been reported due to cross-border movement of gold mining populations. Hiwat outlined primary malaria interventions as targeted outreach and health education to at risk populations; improved provision of malaria services; border screening posts; provision of *Malakit* for self-diagnosis and self-treatment; mass distribution of long lasting insecticide-treated nets (LLINs) among high risk populations; and implementation of National Malaria Elimination plan 2021-2025. She concluded by enumerating important lessons from malaria elimination efforts in Suriname as (i) engaging at-risk populations, (ii) lowering barriers, (iii) remind health workers about malaria through continuous training (iv) integration of malaria programs within existing public health programs, (v) innovation, (vi) in country and cross-border communication and collaboration.



This report is brought to you by the MESA Correspondents Edima Ottoho, Tope Kayode, Franklin Tembongshu Formilack, Lucy W. Mwangi, Vita Mithi, Ana Alonso, Faith Hungwe, Olajoju Temidayo Soniran, Isabelle Delrieu, Doumbe Belisse Patricia and Carlos A. Fernández Miñope, with mentoring and editorial support from Divya Beri.

Discover more content in the Resource Hub

www.mesamalaria.org